THE SPECTRUM OF ACUTE AND SUBACUTE MYELOPATHY

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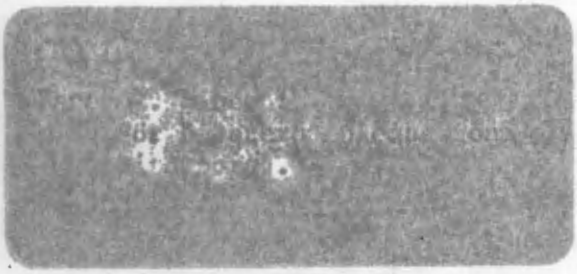

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I am deeply grateful to my parents for their example in combining committed patient care with clinical research.

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SANDY

ABSTRACT

Acute and subacute diseases causing intrinsic spinal cord damage are confusing and poorly defined clinically and pathologically. The purpose of this study is:

1. To analyse the spectrum of conditions responsible for acute and subacute myelopathy in South Africa.

2. To categorise the clinical presentations and prognosis of the illnesses and to correlate these with aetiology.

3. To assess the validity of diagnostic criteria for acute and subacute myelopathy in general and for the different aetiological groups.

4. To review the literature and to correlate previous studies with the present one.

Thirty-four patients fulfilling strict criteria have been identified over a seven and a half year period using the Groote Schuur Hospital computer retrieval system. Although the study was essentially retrospective, 11 of these patients were seen personally during their acute illnesses. All these patients have suffered from illnesses causing spinal cord dysfunction in the absence of trauma, physical agents or any extrinsic presssure such as might be caused by tumours or spondylosis. Maximum disability was reached in less than 8 weeks.

In 17 patients no cause was identified. The clinical features, laboratory findings and courses have been analysed. Among the results, a high percentage of patients with Brown-Séquard Syndromes were found with possible significance for the pathogenesis of the illness.

Seven patients with meningovascular syphilis were analysed as well as 2 additional patients with spinal cord syphilis not fulfilling the strict criteria of the study. Although well known before the penicillin era, this entity is not well described in modern neurological literature. Four patients had myelopathy associated with pulmonary tuberculosis in the absence of tuberculous meningitis or spinal disease. Three of these 4 patients also developed optic neuropathy. The association of these conditions has previously been described in only a very few patients. Two patients had Epstein-Barr virus infections and 1 had an infection with Mycoplasma pneumoniae. Two had systemic lupus erythematosus and 1 had an acute cord infarct following an aortic aneurysm repair.

The literature is reviewed and the findings of this study correlated with previous ones. Conclusions regarding terminology, criteria for diagnosis, investigations, course and prognosis are discussed.

CONTENTS

1. INTRODUCTION

Acute intrinsic spinal cord disease has been recognised since last century. Before the introduction of antibiotics and ventilatory support the condition was considered to be fatal[101] and thus early literature before 1950 consists chiefly of reports of pathological findings.[73,82,112] More recently the prognosis has improved significantly and present literature deals with the clinical features of the condition often with little pathological correlation.

The better known condition of acute inflammatory polyradiculoneuropathy (Guillain-Barré syndrome) provides some peripheral nervous system parallels with acute myelopathy and has been far more extensively studied.[37] In contrast myelopathies have been less vigorously analysed. Idiopathic myelopathies are usually dealt with separately from those with known aetiology and it is difficult to delineate the spectrum of the syndrome from the literature.

1.1. Aims

The aims of this study are:

1. To analyse the spectrum of conditions responsible for acute and subacute myelopathy in South Africa.

2. To categorise the clinical presentations, course and prognosis of the illnesses and to correlate these with aetiology.

3. To assess the validity of diagnostic criteria for acute and subacute myelopathy in general and for the different aetiological groups.

4. To review the literature and to correlate previous studies with the present one.

1.2. Terminology

The terminology of acute spinal cord disease is confusing. The most commonly used term, "transverse myelitis" implies an inflammatory lesion involving both sides of the cord over only a few segments. However, as will be seen, none of these features occur in every case. The term "ascending myelitis" overcomes one difficulty in describing a disease which progresses rostrally to involve many segments longitudinally.[124] However the two terms only denote the geographical localisation and do not add to the clinico-pathological understanding of the illness. "Myelopathy" is a better term than "myelitis" as many acute cord lesions are not inflammatory.

In this study the terms "acute and subacute myelopathy" have been used exclusively to avoid some of the incorrect connotations of other terminology. Just as "peripheral neuropathy" has largely replaced "peripheral neuritis", so the same change should be made for a clearer understanding of cord disease.

1.3. Diagnostic Criteria

It is only in the last 30 years that series of clinically diagnosed cases, the majority of whom have survived, have been reported. In order to compare the results of such studies, it is necessary to give careful attention to the diagnostic criteria used.

Paine and Byers[120] (1953) described 25 cases of transverse myelopathy in children. They did not list any criteria on which the diagnosis was based other than the exclusion of cases with concommitant encephalitis. In 1963

Altrocchi[7] described 67 cases of transverse myelopathy. For the first time certain criteria for diagnosis were laid down. The condition had to develop acutely with intramedullary spinal cord dysfunction not progressing beyond 8 weeks. It could be ascending or static, usually involving both sides of the spinal cord transversely. There should be no previous history of neurological symptoms. Direct trauma, extramedullary compresssion, intramedullary tumours, radiation myelopathy and combinations of spinal cord and cerebral symptoms were excluded. However, myelograms were performed in only 25 of the 67 patients.

These criteria, in many ways arbitrary, have dominated later studies. Lipton and Teasdall (1973) [101] described 34 adults with acutely developing "paralysis of at least both lower extremities, bilateral sensory loss and urinary and faecal retention". Patients with antecendent neurologic and underlying systemic disease were excluded as were all patients with an obvious cause such as herpes zoster, syphilis, trauma or irradiation. In spite of these rigid criteria to obtain a standard clinical picture, 3 different pathologies were found in 6 patients who underwent post-mortem examination (infarction, necrotising myelitis and intramedullary capillary telangiecetasis).

Ropper and Poskanzer (1978)[131] reviewing 52 patients emphasised the importance of a negative myelogram. Their patients progressed over a maximum of 4 weeks, had no antecedent neurological illness and were required to have extensive bilateral spinal cord dysfunction with a well defined upper level. In 2 cases coming to autopsy, different pathology was seen - one a necrotising myelopathy without inflammation and the other demyelination and necrosis with profuse inflammation.

In an epidemiologic Israeli study, Berman et al. (1981)[18] used as criteria an acutely developing paraparesis without progression affecting motor and sensory systems and sphincters, a clear segmental sensory level (excluding Brown-Séquard syndromes) and exclusion of spinal cord compression or any known neurological disease including syphilis and encephalitis. However, viral illnesses such as zoster were included.

Bahemuka (1982)[13] studied 23 case in Kenya. His diagnostic requirements were no previous neurological illnesses, "fairly rapid progression", flaccid or spastic paraplegia with a spinal cord sensory level, no encephalitis and a normal myelogram.

A review of these studies suggests careful attempts to describe a standard clinical picture. However the pathology of acute myelopathy is far from homogenous and, even when the strictest clinical criteria are laid down, the pathology differs. While criteria for acute myelopathy such as progression only over a specific time period and negative myelography are necessary almost by definition, other criteria seem arbitrary and restricting.

An acute myelopathy involving predominantly half the spinal cord may have similar pathology to transverse myelopathy and exclusion of these cases may give a distorted view of the spectrum of the condition. Similarly, it is illogical to include patients who subsequent to acute myelopathy develop optic neuropathy but to exclude those in which optic neuropathy occurs first. Pathological studies have shown that patients with acute disseminated encephalomyelitis[2] may have similar cord pathology to certain patients with acute myelopathy alone. Thus to exclude all patients with evidence of disease above the foramen magnum artificially narrows the disease spectrum.

One of the purposes of this study is to describe a wider spectrum of acute and subacute myelopathy without broadening the conditions beyond recognition.

and was involved in the care of 11 of these patients during the acute phase of their illness. The patients' records were analysed and their later course assessed by personal follow-up examinations, telephonic communication and perusal of hospital records.

Two additional patients with spinal neurosyphilis who did not fulfill the above criteria (1 with an abnormal myelogram and 1 with a chronic history) are also described separately.

2. PATIENTS AND METHODS

The Groote Schuur Hospital computerised record system was used to identify all patients with acute or subacute spinal cord disease admitted between January 1977 and June 1984.

Those patients fulfilling the following criteria were included in the study:

(1) Definite clinical evidence of a myelopathy as shown by upper motor neurone type weakness of the legs with increased tone and brisk tendon reflexes and/or a definite sensory level usually on the trunk. In the case of those patients with flaccid areflexic paraplegia ("spinal shock"), a sensory level was considered essential.

(2) Progression of the disease to a maximum disability in less than 8 weeks.

(3) Either (a) a normal myelogram or

(b) a myelogram showing cord swelling over more than 10 segments or

(c) in the absence of a myelogram, complete clinical recovery or

(d) in the absence of a myelogram, an obvious aetiology such as meningovascular syphilis.

(These criteria excluded all cases of myelopathy associated with cervical spondylosis, arachnoiditis and compressive lesions).

(4) An absence of direct trauma or physical agents such as radiotherapy.

(5) No prior diagnosis of multiple sclerosis according to standard criteria.[126]

Thirty-four patients fulfilling these criteria were identified. Although this was essentially a retrospective study, I personally examined

3. GENERAL RESULTS

A few general results are given below. Because of the aetiological heterogeneity of the group, the results are analysed in detail later under each category:

(1) Idiopathic Myelopathy.

17 patients

(2) Meningovascular Syphilis of the Spinal Cord.

7 patients

(3) Myelopathy associated with Pulmonary Tuberculosis (PTB).

4 patients

(4) Myelopathy associated with other specific infections.

3 patients

(5) Systemic Lupus Erythematosus (SLE) - related myelopathy.

2 patients

(6) Spinal Cord Infarction.

1 patient

In each category, selected case reports with comments are presented first, followed by an analysis of the results and thereafter discussion.

Owing to the fact that Groote Schuur Hospital has few paediatric beds, all patients are over the age of 13 years. Eleven patients were white, 19 coloured and 4 black. Cape Town, with a large coloured and relatively smaller black population, is not representative demographically of South Africa as a whole and thus extrapolations from these figures should be made with caution.

Of the 34 patients, 29 had normal myelograms. Four did not have myelograms, 2 because complete recovery occurred and 2 because the diagnosis

was clinically obvious (1 with serological evidence of neurosyphilis and 1 with a spinal cord infarct following aortic aneurysm surgery). One patient showed cord swelling from the 2nd cervical to the 9th thoracic segment on myelogram.

In view of certain previous studies having excluded patients with preceding or concommitant neurological disease localised elsewhere than in the spinal cord, such cases that are included in the present study are briefly discussed. In only 3 patients was there preceding neurologic disease. One patient with neurosyphilis had had a preceding midbrain syndrome and 2 patients with neuromyelitis optica associated with tuberculosis had developed optic neuropathy before the myelopathy.

In 5 patients the myelopathy was associated with concommitant neurologic disease. One patient with idiopathic myelopathy had extensive brainstem involvement and another patient in this group had bilateral facial weakness. One patient with SLE-related myelopathy had transient bulbar weakness. One patient with mycoplasma associated myelopathy had mild bulbar weakness and one seizure and one patient with infectious mononucleosis associated myelopathy had a demyelinating peripheral neuropathy.

4. IDIOPATHIC MYELOPATHY

4.1 Case Reports

Four case reports selected from 17 patients are described.

Case No. 1.

A 62 year old previously well white male developed left iliac fossa pain in February 1983. Three days later the pain spread from the midline around the left flank to the spine and he noticed skin sensitivity in a band over the 9th left thoracic dermatone. This lasted 5 days and resolved. The following day (day 10 of his illness) he noticed numbness of his right leg and 24 hours later weakness of his left leg with difficulty initiating micturition and defaecation. By day 13 his left leg was completely paralysed and urinary retention necessitated catheterisation.

Abnormal physical findings was limited to the legs. The left leg was flaccid, areflexic and completely paralysed. The right leg was slightly weak (grade 3-4/5 power).[5] There was a sensory level below which pain and touch sensation were absent at the 8th right thoracic dermatome (T8). Position sense was normal. Anal tone was reduced. By day 16 his condition had progressed to a complete bilateral flaccid areflexic paralysis with a sensory level for all modalities at T8 bilaterally.

Cerebrospinal fluid (CSF) examination on day 14 showed a protein concentration of 0.9 g/l, 2 + globulin, 10 lymphocytes mm^{-3} and a normal glucose concentration. A repeat lumbar puncture 10 days later showed a protein concentration of 1,4 g/l, a trace of globulin, 25 lymphocytes, 1 neutrophil mm^{-3} and a normal glucose concentration. Stains for fungi and bacteria were negative. No viruses were cultured and there was no significant rise in viral antibodies, specifically to herpes zoster. Syphilitic serology was negative.

A myelogram was normal. All serum immunological tests for specific organisms and auto-antibodies were negative. The erythrocyte sedimentation rate (ESR) was 27 mm in the first hour and the white cell count was normal.

Acyclovir was administered intravenously for 5 days. The course was complicated by urinary tract infection, pressure sores and severe depression. Power and sensation did not return, but he slowly developed hypertonia and hyperreflexia. He died 7 months after onset of his illness in another hospital from undetermined cause.

Comment

This patient illustrates the progression of a myelopathy transversely across the spinal cord, commencing with root pain and progressing through a Brown-Séquard syndrome to a complete myelopathy with initial spinal cord shock. In spite of the lack of skin lesions, herpes zoster was considered as a possible cause because of the mode of onset, and acyclovir was administered with no response.

Case No. 2

A previously well 43 year old coloured male developed mid-thoracic backache in July 1981. One week later he developed a cold sensation in his right leg which worsened until admission on the 14th day of his illness. He developed urgency incontinence and constipation.

On examination cranial nerves and arms were normal and there was no spinal tenderness. Tone was increased in the left leg with power reduced to grade 1-2/5. Power in the right leg was minimally reduced (grade 4-5/5). There was a sensory level at T5 on the right below which touch, pain, temperature and vibration sense were absent. Position sense was normal bilaterally.

CSF examination of day 17 showed a protein concentration of 0.5 g/l, no globulin, 11 neutrophils and 36 lymphocytes mm^{-3}. A repeat study 9 days later showed a protein concentration of 0,2 g/l and 30 lymphocytes mm^{-3}. Glucose concentration was normal. Culture for bacteria, fungi and viruses was negative as was syphilitic serology.

Myelography was normal. Serum immunologic tests for infective organisms and auto-antibodies were negative. The ESR was 5 mm in the first hour and the white cell count was normal.

No specific treatment was given. By 3 months after onset, power was improved and bladder function and sensation normal. By 8 months he had returned to work and complained only of constipation. The only abnormal signs were slight weakness of ankle dorsiflexion bilaterally and leg hypertonia and hyperreflexia.

Comment

This patient illustrates the onset of a myelopathy heralded by backache. The picture remained that of a Brown-Séquard syndrome with sparing of position sense. Fair recovery occurred with residual upper motor neurone signs.

Case No. 3

A 33 year old previously well black male developed a 7 day febrile illness with cough and sore throat in October 1983. Two days after it resolved, he developed weakness and numbness of both legs. Over 7 days this progressed to a complete paraplegia with urinary retention needing catheterisation.

On examination, cranial nerves and arms were normal. There was a complete areflexic flaccid paraplegia with a T8 sensory level below which all sensation including position sense was lost. He had a flaccid anal sphincter.

CSF examination one day after onset showed a protein concentration of 0,2 g/l, no globulin, 16 lymphocytes mm^{-3} and 13 neutrophils mm^{-3}. A repeat study 2 weeks later showed a protein concentration of 0,7 g/l, 2 + globulin, 245 lymphocytes mm^{-3} and 60 neutrophils mm^{-3}. A third study 2 months after onset showed a protein concentration of 3,0 g/l, 1 + globulin and 23 lymphocytes mm^{-3}. Glucose concentration was normal in all 3 specimens. Culture for bacteria, fungi and viruses were negative, as was syphilitic serology.

A myelogram was normal. All serum immunological tests for infective agents and auto-antibodies were negative. The ESR was 40 mm in the first hour and the white cell count was normal.

No specific treatment was given. His course was complicated by urinary infection and pressure sores. He remained completely paraplegic and when examined 10 months after onset still had flaccid areflexic legs. Electromyography (EMG) 2 months after onset showed positive sharp waves and fibrillations in quadriceps, tibialis anterior and extensor hallucis brevis bilaterally.

Comment

This patient illustrates the onset of an acute myelopathy following a non-specific upper respiratory infection. The patient remained areflexic and flaccid with an EMG suggesting extensive denervation. Thus he appears to have had a longitudinal myelopathy with extensive damage at all levels below

T8. Of interest is the rise in CSF protein concentration 2 months after onset.

Case No. 4

A previously well 22 year old white female developed decreased perception of pain in her right leg in April 1984. The next day weakness developed in her left leg and that evening she began vomiting. On day 3 of her illness drowsiness developed and by day 5 her left leg was so weak she could not walk. On day 7 her speech became slurred, she noticed diplopia and oscillopsia and her left hand became weak. The next day the right side of her face became numb and she noticed loss of taste. On day 13 she developed urinary retention. A myelogram was performed, which was normal and she was transferred to Groote Schuur Hospital.

On examination on day 14 she was drowsy but orientated. There was bilateral ptosis. Horizontal nystagmus was induced on looking to the right and vertical nystagmus on elevating the eyes. Fundi and pupils were normal and eye movements full. There was decreased sensation over the right side of the face and taste was diminished over the anterior two-thirds of the right side of the tongue. There was bilateral lower motor neurone type facial weakness. Sensation was diminished on the right side of the pharynx and there was bilateral pharyngeal weakness. The tongue was weak bilaterally but not fasciculating.

There was a hypertonic, hyperreflexic weakness of the left arm (grade 3-5/5) and the left leg (grade 0-2 /5). Power on the right was normal except for mild weakness of the leg. Tendon reflexes on the right were also brisk and both plantar responses were extensor. There was a sensory level at T4 on the right below which touch, pain and temperature were absent. There was

decreased position sense in the left foot and decreased vibration sense in both ankles and the left hand.

CSF examination on day 14 showed a protein concentration of 0.45 g/l, no globulin, 4 lymphocytes mm^{-3} and normal glucose concentration. The CSF IgG quotient [100] was suggestive of local IgG synthesis as well as blood-CSF barrier impairment. Viral studies were negative. Blood immunological tests for infections or auto-immune illnesses were negative. An electro-encephalogram (EEG) showed diffuse theta activity.

By day 21 both legs and the left arm were completely paralysed and she had become increasingly drowsy. Bulbar functions decreased and respiratory difficulties necessitated tracheostomy and supportive ventilation. A course of acyclovir was administered and thereafter corticosteroids.

On day 24 recovery commenced and she was weaned from the ventilator one month after admission. By day 52 she was mentally normal. Cranial nerves were normal except for mild bilateral facial weakness and a partial left 12th cranial nerve palsy. Power in both arms was grade 4-5/5, in the right leg 3/5 and the left leg 2/5. There was mild spasticity in the legs with hyper-reflexia. Apart from decreased position sense in the left foot, sensation was normal.

Comment

This case illustrates the simultaneous development of an acute myelopathy and acute brainstem disturbance, and belongs in the spectrum of acute disseminated encephalomyelitis.[106] The evidence for myelopathy is the Brown-Séquard nature of the signs on admission with a clear unilateral thoracic sensory level for pain and temperature and contralateral weakness and position sense loss. Midbrain, pons and medulla were involved and this

aspect of the illness was similar to Bickerstaff's brainstem encephalitis.[19] As in Bickerstaff's series, the patient made a remarkable recovery suggesting that the major pathology was demyelination rather than necrosis.

4.2. Results

4.2.1 Age, Sex and Race

The mean age at onset was 36 years (range 16-62 years). There was no sex predominance (8 male, 9 female). Six patients were white, 10 coloured and 1 was black.

4.2.2 Preceding illness

Four patients (24%) had preceding infectious illnesses (3 upper respiratory infection, 1 fever, malaise and arthralgia). One patient had antecedent minor back strain and 1 had undergone a hysterectomy 6 weeks before. Eleven patients (54%) had no antecedent events. There was no seasonal preponderance.

4.2.3 Onset

In 6 patients (35%) sensory symptoms were the initial complaint - numbness, paraesthesiae or temperature disturbance. In 7 patients (41%) pain occurred first - 3 with backache and 4 with radicular pains in a thoracic distribution. In 1 patient (6%) weakness occurred first and in 1 sphincter disturbance. In 2 patients combinations of symptoms started simultaneously - 1 motor and sensory and 1 motor, sensory and sphincter disturbance.

4.2.4 Initial course

Patients were divided into 3 groups according to the course of the

disease (classification of Ropper and Pozkanser).[131] Ten patients (59%) followed a smoothly progressive course to maximum disability. Six patients (35%) followed a stuttering course with the illness stabilising before a new symptom developed. One patient (6%) followed a hyperacute course with maximum disability in less than 1 hour.

The following table shows the time from onset to maximum disability:

Time	Patients
Less than 1 hour	1
1 - 12 hours	0
12 - 24 hours	1
1 - 2 days	1
2 - 7 days	3
8 - 14 days	4
2 - 3 weeks	4
3 - 4 weeks	1
4 - 5 weeks	0
5 - 6 weeks	2

4.2.5 Symptoms and signs

Fever occurred in 6 patients (35%), 2 of whom had secondary infections (1 urinary, 1 pneumonic). Spinal tenderness was present in only 1 patient. None had neck stiffness.

Pain was a feature of some stage of the illness in 10 patients (59%). Five had backache alone, 3 radicular pain alone and 2 both.

Weakness occurred in all 17 patients. In 5 patients (29%) a flaccid paraplegia with areflexia ("cord shock") developed. In 12 patients (71%)

increased tone and brisk reflexes were present from the start. Of these 12, 7 had grade 3-4/5 power in the legs,[5] 3 had grade 1-2/5 power in at least 1 leg and 2 had complete paraplegia. In 5 of the 17 patients, arm weakness also occurred in spite of a clear thoracic sensory level. Two of the 5 patients showed some brainstem involvement.

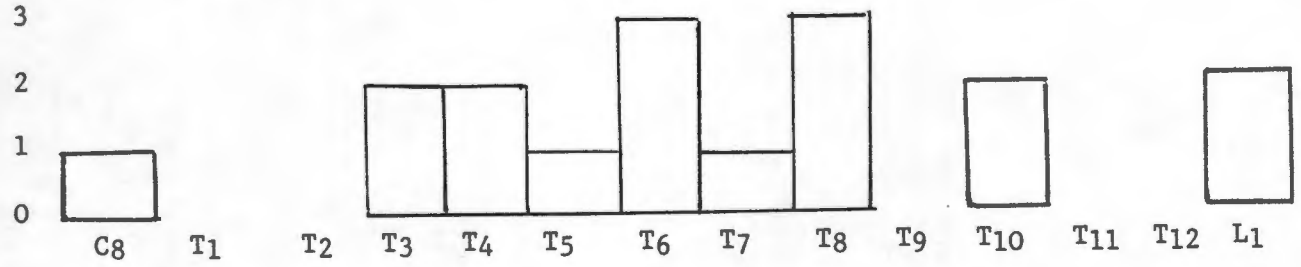
In all 17 patients sensory loss occurred in the legs. In all 17 disturbance of pain and temperature sensation was found and in 9 position sense was also disturbed. In 2 patients sensation was abnormal in the hands although there was a clear thoracic sensory level.

A notable feature was the high proportion of Brown-Séquard syndromes. In 5 patients either the motor signs were purely unilateral or grossly asymmetrical with spinothalamic sensory loss confined to the contralateral side. In 2 of these 5 patients position sense was lost, 1 on the same side as the motor disability and 1 bilaterally. In 1 patient the sensory signs were suggestive of unilateral cord disease (spinothalamic and posterior column loss in opposite legs) although the motor signs were bilaterally symmetrical. In 1 patient (case No 1) the illness started as a Brown-Séquard syndrome and progressed to a complete transverse lesion. In another patient (case No 4) an initial Brown-Séquard syndrome progressed to complete paralysis with the sensory findings remaining dissociated. Thus 8 patients (47%) at some stage of the illness showed evidence of predominantly unilateral cord involvement.

Sphincter disturbance occurred in 13 patients (76%). All these had urinary problems with 9 having retention needing catheterisation, 1 developing only loss of bladder sensation and 1 urgency only. Nine of these had anal sphincter disturbance - 7 had a flaccid anus with incontinence and 2 constipation only.

4.2.6 Sensory level

All 17 patients had clear spinal cord segmental sensory levels for pain, although 5 patients had mild arm weakness above the sensory level. The levels are shown in the following chart.



4.2.7. Laboratory Results

Myelograms were normal in 15 patients. In 2 patients myelograms were not performed, but both made a complete recovery without specific treatment.

CSF was examined in all 17 patients. In 12 patients the CSF protein concentration was normal, in 5 patients it was raised on at least 1 occasion (range 0,5-3,0 g/l). A pleocytosis was found in 10 patients on at least one occasion (range 7-305 cells, all but 1 under 50 cells). In all 10, lymphocytes predominated. In 7 patients CSF was completely normal.

Repeat lumbar punctures were performed on 6 patients. In 3 patients, the CSF protein concentration rose - in the first patient from 0,9 g/l 2 weeks after onset to 1,4 g/l over 10 days; in the second from 0,6 g/l 3 weeks after onset to 4,0 g/l over 14 days and in the third from 0,2 g/l 1 day after onset to 0,7 g/l after 2 weeks and then to 3,0 g/l after another 6 weeks. All 3 of the patients presented with spinal shock. (The remaining 2 patients with spinal shock had only 1 lumbar puncture each - 1 had a normal protein concentration and the other a protein concentration of 0,7 g/l). In the

other 3 patients who underwent a second lumbar puncture, the protein concentration remained normal in 2 and dropped from 0,5 g/l to normal in the third. All 3 had hyperreflexia and hypertonia from onset.

The CSF of the 6 patients who underwent repeat lumbar punture showed no significant change in the cell count in 2, a fall in 1 and a rise in 3. These changes did not parallel changes in CSF protein concentration. (e.g. 305 cells mm^{-3} falling to 23 cells while CSF protein concentration rose from 0,7 g/l to 3 g/l).

CSF glucose concentration was normal in all patients. CSF IgG/albumen ratios were measured in 5 patients. Four showed a normal ratio. In case No. 4 (with associated brainstem disease) the CSF IgG gradient suggested local IgG synthesis as well as blood-CSF barrier breakdown. Lange colloidal gold curves were performed in 4 patients - 1 was normal and 3 showed a first zone reaction. All stains and viral cultures of CSF were negative. CSF cytology was negative and cryptococcal antigen absent in all patients.

The ESR ranged from 5 to 140 mm (all but 3 were under 50). White cell counts were normal, except for patients with complicating infections. Tests for complement, anti-nuclear factor (ANF), rheumatoid factor, Epstein-Barr virus, mycoplasma, herpes zoster and cytomegalovirus antibodies were all negative.

In 4 patients blood syphilitic serology was positive. In the first case, the Venereal Disease Research Laboratory (VDRL) test was positive to a titre of 1 and the fluorescent treponema antibody absorption (FTA-abs) test was positive. However the CSF was normal with negative VDRL and the patient later progressed to multiple sclerosis. Two patients had negative blood VDRL's but positive treponema pallidum haemagglutination test (TPHA). In one

the CSF was normal and he recovered fully without penicillin. In the other the CSF had 10 lymphocytes mm^{-3} but the CSF VDRL was negative and the patient also improved without penicillin. The 4th patient had a blood VDRL positive to a titre of 4 with positive blood TPHA. However, CSF was normal and CSF VDRL negative. No penicillin was given and no improvement occurred. None of these patients were thought to have neurosyphilis at the time and illustrate some of the diagnostic difficulties that arise in a population with a high prevalence of latent syphilis. This aspect will be discussed in detail later.

4.2.8. Management, Complications and Outcome

Four patients received prednisone, 1 ACTH and 2 acyclovir. There was no convincing response.

The early course was complicated by pneumonia in 1, urinary tract infection in 4, pressure sores in 3 and respiratory failure in 1.

Two patients died, one from pulmonary emboli 8 weeks after onset and 1 from undetermined causes. Of the remaining 15 patients, 2 could not be traced after discharge. The remaining 13 patients were followed for an average of 3 years 1 month (range 1 month - 7 years). Only 5 patients were followed for less than 1½ years - 2 made a full recovery (follow-up 1 month and 6 months), 1 a fair recovery (follow-up 5 months) and 2 remained densely paraplegic (follow-up 10 months each). No patient continued to improve beyond 18 months.

Recovery was assessed in terms of the criteria of Lipton and Teasdall.[101] Good recovery implied normal gait, minimal if any abnormal neurologic signs and micturition either normal or with minimal urgency. Fair recovery implied ambulation but with a spastic gait. Urgency of micturition

and constipation were frequently present and signs of spasticity and abnormal sensation were present. Poor recovery implied lack of ambulation with severe paraplegia and absence of sphincter control. Six patients (46%) made a good recovery, 5 a fair recovery (38,5%) and 2 a poor recovery (15,5%).

Two patients developed multiple sclerosis by standard criteria[126] and 1 developed unilateral optic neuropathy 1 month after the onset of myelopathy (neuromyelitis optica).

Outcome did not correlate with age, sex, sensory level, previous infection nor type of progression. However, both patients with poor outcomes presented with spinal shock, as did one patient who showed no recovery at time of death. Only 1 out of 11 patients with good or fair recovery presented with spinal shock. The relationship of CSF to severity has been described earlier.

4.3. DISCUSSION

4.3.1 Clinical Aspects

A. General

The age range and lack of preponderance of either gender are similar to previous studies, as is the lack of relationship to seasons. The first symptom varies markedly but the commoness of pain must be emphasised. In this series it was the presenting complaint in 41%, similar to the 35%[131], 45%[101] and 46%[7] in previous studies. In any patient with an acute cord syndrome, space-occupying lesions must first be excluded but the presence of pain does not specifically point to a compressive pathology.

B. Level

All but 3 patients had a thoracic sensory level with the commonest site

being between T_6 and T_8. This is in keeping with previous studies.[7,13,18,101,120,131] The thoracic cord has the most precarious blood-supply (see later) and this has been postulated as the reason for its vulnerability.

C. Cerebro-spinal Fluid (CSF)

The CSF was abnormal in 59% of patients, which correlates well with a previous report of 62%.[18] In general, the cell count is usually less than 300 mm^{-3} with a lymphocytic predominance[131] but isolated cases are found with extremely high counts (e.g.8800 cells)[7] and with a marked neutrophilic predominance (e.g. 94%.[131]) Protein concentrations can be raised up to 5g/1.[18]

In the present study, an interesting finding was the marked rise in CSF protein concentrations in 3 patients presenting with spinal shock. Repeat analyses in 3 other patients with initial hyperreflexia and hypertonia did not show a rise. Although the numbers are too small to reach any firm conclusion, a possible correlation may exist and further prospective studies are needed. Only 2 previous studies have commented on follow-up CSF analysis. Ropper and Poskanzer[131] noted "2 patients with initially normal CSF protein had elevated protein when retested within 1 year" but give no further details. Paine and Byers[120] found no consistent pattern.

D. Outcome

Although the period of follow-up was relatively short, no patients continued improving beyond 18 months. Of the 5 patients followed for less than that time, 2 recovered fully and 1 partially.

The only correlate with poor outcome was spinal shock, a finding

previously noted.[101,131] The 1 patient with a hyperacute onset had a poor outcome in keeping with Ropper and Poskanzer's findings.[131] This study does not confirm their finding that backache correlated with poor outcome.

4.3.2. Pathology

It must be immediately recognised that the clinical spectrum of acute idiopathic myelopathy represents more than 1 pathological process. Early studies grouped together similar pathological entities whereas later studies described similar clinical pictures. Even today there is no clear formulation of the relative frequencies of different pathologies and their clinical correlations. As the prognosis improves with better supportive care, so less pathological material is available. In the present study only 2 patients died and no autopsies could be obtained. In addition any pathological study is biased by the fact that only the more severe cases die and thus the milder cases are under-represented.

In most cases the pathology falls into 1 of 2 groups with a spectrum showing some features of both.

Firstly, a number of pathological studies have been reported describing a condition called variously progressive necrosis of the spinal cord,[112] spinal necrosis and softening of obscure origin,[82] acute myelomalacia and acute necrotic myelopathy.[73] Clinically the picture has been that of a severe acute or subacute myelopathy. The basic pathology is an extensive necrosis of the grey and white matter of the cord often over a considerable longitudinal extent. The large anterior and posterior spinal arteries are patent, but in about 65% of autopsies[73] medial and intimal hyperplasia has been noted in small intramedullary arteries and in some case also in larger

ones on the spinal cord surface. Thickening of the walls of small veins has also been noted.[58]

Secondly, some patients are found to have a predominantly demyelinating lesion with perivenous round cell inflammatory infiltrate.[2] This is similar to the histology seen in acute disseminated encephalomyelitis (ADE) which can follow vaccination or infections including measles, mumps, rubella and varicella.[100,106] This in turn is similar to the histology seen in most cases of experimental allergic encephalomyelitis (EAE). This illness is induced by the injection of central nervous system basic encephalogenic protein (BE-protein) (one of the major components of CNS myelin) into laboratory animals. It is mediated chiefly by a delayed hypersensitivity T-cell response and provides the best animal model available for the study of acute myelopathy.[110]

The significance of these changes for an understanding of possible aetiologies will now be discussed.

4.3.3. Aetiological Factors

A. Vascular Factors

(1) Anatomical background

The arterial blood-supply of the spinal cord comes from 3 longitudinal trunks and a number of segmental feeders.[105]

(a) Anterior spinal artery.

This arises from branches from the vertebral arteries which fuse to form a single vessel running downwards on the midline of the anterior surface of the cord. The general direction of blood flow is caudally.

(b) Posterior spinal arteries.

These arise from the posterior inferior cerebellar arteries (2/3 of cases) or vertebral arteries (1/3 of cases). They run downwards in the form of anastomosing networks at the dorsal root entry zones.

(c) Segmental arteries

Each nerve root has a radicular artery arising from a segmental trunk artery e.g. in the dorso-lumbar region the radicular artery arises from the intercostal and lumbar branches of the aorta.(35) These radicular arteries form 2 anastomatic nets, an outer net over the vertebral bodies and an inner net extradurally.

Only a very few of the radicular arteries extend sufficiently far inwardly to join the longitudinal spinal arteries.(144) However, these few feeders are vital to maintaining the blood-supply of the cord as the descending arteries by themselves carry insufficient blood. Approximately 8 feeders (range 2-17) augment the anterior spinal artery and 12 (range 6-25) augment the posterior spinal arteries.(35) Most of these feeders join in the cervical and lumbar areas leaving the upper and mid-thoracic segments least supplied.(144) In the thoraco-lumbar area there is one major feeder known as the Artery of Adamkiewicz (arteria radicularis magna). This is on the left in 60-80% of persons and usually accompanies a root between T_9 and T_{11} (range T_8 -L_4).(35)

The anterior spinal artery gives rise to central sulcal arteries which run posteriorly in the anterior median fissure and then divide to supply either the right or left side of the cord. Successive arteries run to alternate sides.(68) These are end arteries and do not anastomose, but the capillary beds of successive arteries overlap longitudinally running as much

as 3 cm up and down in the thoracic area.[152] They supply the central portion of the anterior 2/3 of the cord (grey matter and inner white matter).

The posterior spinal arteries give rise to penetrating branches which supply the dorsal columns and the posterior horns. A pial network formed from the anterior and posterior arteries is found on the cord surface and this supplies the superficial white matter by radial branches.[105]

(2) Clinical Evidence

(a) Dissociated sensory loss

The preservation of position and vibration sense in many cases has been taken as evidence for the vascular nature of the lesion as this would fit the anatomical site corresponding to "anterior spinal artery occlusions." Lipton and Teasdall[101] found dissociated sensory loss in 10 out of 34 patients and Paine and Byers[120] in 10 out of 25 children. However Ropper and Poskanzer[131] found only 1 patient out of 52 with preservation of position sense at onset and Altrocchi[7] found dissociated loss in only 9 out of 67 patients. Thus the percentage of patients in the literature with preservation of posterior column sensation ranges between 2% and 40%.

In the present series position sense was spared in 8 out of 17 patients (47%). This higher percentage probably reflects only the diversity of disease manifestations rather than indicating a vascular aetiology. Obviously those series with stricter criteria requiring severe transverse cord lesions will have a higher percentage with posterior column involvment. I believe the present study provides a fairer representaton of the disease spectrum.

(b) Brown-Séquard Syndromes

An important finding of this study has been a high percentage of predominantly unilateral cord disease. Seven patients had variants of a Brown-Séquard syndrome, 4 with posterior column loss. A further patient commenced with a Brown-Séquard syndrome and progressed to a complete transverse lesion.

Among the more recent large series, only Paine and Byers[120] have mentioned 3 similar cases without adequate clinical details. McAlpine[106] in 1931 alludes to Brown-Séquard syndrome in acute myelopathy. Cosnett[27] describing 5 South African blacks with neuromyelitis optica noted that 2 had pictures suggestive of Brown-Séquard syndrome.

Paine and Byers[120] feel these cases represent occlusion of a single central sulcal artery causing unilateral cord disease. On the contrary I feel that they are evidence against a vascular theory. Firstly, the posterior columns should have been preserved as they are supplied by the posterior spinal arteries and not the central sulcal arteries Secondly, there is considerable overlap as noted before between the longitudinal territories of supply of the central sulcal arteries. Thirdly, the patient whose illness progressed from root pain via a Brown-Séquard syndrome to a transverse myelopathy could not possibly have had a vascular aetiology - it is inconceivable that the central sulcal artery supplying the contralateral side of the cord at the same level should occlude at exactly the appropriate time to cause a smooth clinical progression.

(c) Other

The sometimes relatively slow onset and ascending nature of the disease have been used as arguments against a vascular cause. However the unusual

clinical pictures described with atheromatous cord infarction[79] make these arguments less impressive (see below for further details).

(3) Pathological Evidence

Since last century certain pathological studies have led many authors to postulate that acute myelopathies are vascular in origin.[120] In 1902 Singer[140] found that 17 out of 19 cases of so-called acute myelitis had apparently either syphilitic or atheromatous vascular disease. Since then the pendulum has swung away from this aetiology but pathological evidence in its favour needs discussion.

(a) Acute Necrotic Myelopathy

As described above the large vessels in this condition are patent, but in about 2/3 of cases small vessels show hyperplasia of their walls. These features have been quoted in support of a vascular origin for the pathology, but today most authors[73] feel they are probably due to the same insult that causes the myelopathy. Certainly the 1/3 of cases of acute necrotic myelopathy without vascular changes do not differ in any other pathological or clinical way from those with them.

(b) Atheromatous spinal cord infarction

A different approach to this problem is to examine studies of spinal cord infarction due to atherosclerosis and to compare the clinical picture with that of idiopathic myelopathy. In spite of the restricted nature of the cord blood-supply, spinal cord infarction is rare. No cases were found in an autopsy study of 3737 examinations performed between 1909 and 1958 at the National Hospital for Nervous Diseases, London.[52]

However more recent clinico-pathological studies have generally agreed

on the following aspects:

(i) The clinical picture is often subacute or chronic rather than acute.[79]

(ii) The anterior and posterior spinal arteries are remarkably preserved from atheroma. Jellinger[85] found in 1037 unselected autopsy cases atherosclerosis in major spinal cord arteries in only 12,7%. This was mild or moderate non-stenosing in 12,3% and showed obstruction or plaque formation in only 0,4%. Atheroma of the radicular feeding arteries or small intramedullary arteries was even rarer. In one French study[63] of 19 spinal cord infarcts, the anterior and posterior spinal arteries were normal in all.

(iii) The major cause of atheromatous cord infarction is disease of the segmental arteries where they leave the aorta either due to atheromatous plaques or aortic aneurysms.[52,69,79] The origin of these arteries from the aorta is at a 90 degree angle and thus partial occlusion of the orifices may lower distal pressure more than if the angle was more obtuse.[85]

(iv) The site of cord infarction is variable and does not always follow clear-cut vascular territories. Conventional "anterior spinal artery syndrome" infarction does occur but it is not the rule and almost never seems to be due to atheromatous anterior spinal artery thrombosis. In some patients watershed infarction between anterior and posterior spinal artery territory has been found.[52]

(v) In addition to aortic disease, emboli and hypotension have been reported as causes.[52]

Thus these studies provide little evidence by extrapolation from atheromatous disease for a vascular theory for most cases of acute idiopathic myelopathy.

(c) Definite vascular lesions.

Some cases of acute myelopathy are undoubtedly due to vascular causes but these entities are the minority. Lipton and Teasdall[101] found an unexpected intramedullary capillary telangiectasis with haemorrhage in one spinal cord at autopsy and Altrocchi[7] reported 1 arteriovenous malformation found at laminectomy in his series of 67 patients. Mair and Falkerts[104] described a patient with extensive longitudinal thrombophlebitis of the anterolateral venous system of the spinal cord with patchy cord infarction and normal arteries.

B. Infective factors

There is considerable evidence that at least some cases of acute idiopathic myelopathy are related to infections.

(1) Relationship to non-specific infectious illness.

Twenty-five percent of illness in the present study were preceded by an upper respiratory or non-specific viral type infection. In the 6 reported series this percentage is 16%,[7] 30%,[13] 31%,[131] 35%[18,101] and 60%[120] (the last in a series consisting only of children).

(2) Similarity to acute myelopathy after infections by a specific pathogen.

Acute myelopathy has been reported after many viral illnesses including measles, rubella, chicken-pox, mumps,[109] influenza,[124] infectious mononucleosis,[138] polio, coxsackie B,[13] herpes zoster[74] and herpes

simplex[95] infections. Mycoplasma related myelopathy also occurs.[159] In most cases the clinical picture is indistinguishable from idiopathic myelopathy.

(3) Relationship to vaccination.

Myelopathy following vaccination against polio[131], small-pox,[18] rabies and tetanus[124] have been reported.

(4) Clinical features

Occasional patients have been reported with both an inflammatory polyneuropathy (Guillain-Barré syndrome) (GBS) and an acute myelopathy.[51,138] The most commonly accepted hypothesis of GBS pathogenesis is that of an autoimmune process often post-infectious.[1,100] Its occurrence with acute myelopathy suggests the two may have similar mechanisms.

The Brown-Séquard syndromes reported in the present study, especially the patient who progressed from radiculopathy to a complete transverse myelopathy, (case no 1) seem compatible with an inflammatory process. One might hypothesise, with herpes zoster as a model, an initiating factor infecting first a nerve root and then the spinal cord transversely. However, as discussed below, herpes zoster has only once been isolated from spinal cord tissue and such direct infection probably only occurs in a minority of cases.

(7) Nature of the pathology

As discussed above, the demyelinating form of acute myelopathy with perivenous inflammation resembles the pathology of ADE. This illness can follow measles, mumps, rubella, varicella and infectious mononucleosis,[100]

a list similar to the viral cases of acute myelopathy alone. Of special interest is case 4 in the present series where a cord and brainstem lesion evolved simultaneously. The histology of ADE is close to that of EAE and this similarity to an undoubtedly immune mediated illness provides further support for the possible role of infective factors in acute myelopathy.

Even the alternative pathology of acute necrosis with little inflammation is similar to the hyperacute necrotising form of EAE.[1] This form is induced by injecting brain tissue combined with adjuvant and pertussis vaccine.[100] A further clinical condition with again similar histology is acute haemorrhagic leucoencephalitis which follows a non-specific viral illness in 50% of cases.[110]

(6) Lymphocyte transformation studies.

Apart from exceptional cases[74,88,95] viruses are not isolated from the CSF or spinal cord of patients with acute myelopathy[124] and the most plausible explanation is that a hypersensitivity reaction induced by the virus results in demyelination or necrosis. This may occur either as a parainfectious or postinfectious event.

In one study[1] 7 out of 10 patients with acute myelopathy showed lymphocyte transformation in vitro in response to BE-protein and 3 out of 8 to P2 basic protein (found in peripheral nerve but similar to CNS BE-protein). No response occurred to PIL protein (found in peripheral nerve and purely neuritogenic) and none to acetylcholine receptor. No response occurred on retesting 6 patients some months after the acute event. Seven out of 9 patients with Guillain-Barré syndrome showed lymphocytic transformation to PIL protein only and controls with other neurological diseases showed no response to the antigens used. This suggests that the

response seen is relatively specific for cell-mediated cord damage but it is still unsure whether it represents the primary event or a secondary epiphenomenon.

C. Relationship to Multiple Sclerosis (MS)

Two of the 16 patients in the present series developed MS and an additional 1 developed unilateral optic neuropathy (19%). In previous studies, 2%,[18] 3%,[101] 6%[7] and 13%[131] progressed to MS or neuromyelitis optica. The slightly higher percentage in our study is interesting in view of the low incidence of MS in South Africa.[8] In general, acute myelopathy rarely progresses to a more generalised demyelinating disease.

D. Other Factors

Minor trauma sometimes precedes the onset of a myelopathy[7] as occurred in 1 of our patients. Toxins and drugs have been implicated including arsenicals, orthocresylphosphate, iodoxyquinoline, intrathecal penicillin[124] and heroin.[55] Unrecognised toxic or dietary factors have been postulated in the pathogenesis of chronic idiopathic myelopathy in South Africa.[26,156] (Collagen vascular disease and systemic neoplasia are discussed later).

E. Conclusions regarding Aetiology

Much uncertainty still remains. However present evidence suggests that the majority of acute idiopathic myelopathies represent a spectrum of immune reactions of the spinal cord to unknown external agents, many of which may well be infectious. A minority of cases are vascular in origin and a few represent the first episode of multiple sclerosis.

4.3.4 Therapy

No adequate clinical trials have been performed on the use of steroids in acute idiopathic myelopathy. Anecdotal reports of their uncontrolled use in a few patients[36] give little assistance. The only controlled trial[119] compared oral and intramuscular steroids, intrathecal steroids and "antibiotics". The diagnostic criteria were inadequate, the trial does not appear to have been randomised or blinded and the clinical details were scanty. The authors found a statistically significant improvement only with intrathecal steroids but the design errors make the results worthless.

At present there are no guidelines that can be offered and clinicians should judge each case individually. If steroids are used, they should not be continued for long periods if there is no clinical response.

5. SYPHILITIC MYELOPATHY

5.1. Case reports

Seven patients with acute or subacute myelopathy due to neurosyphilis have been identified. Three representative case reports with comments follow.

Case No. 5.

A 24 year old black male was treated at a venereal disease clinic for a urethral discharge in February 1983. Venereal Disease Research Laboratory test (VDRL) was negative. In July 1983 he developed coldness and disturbed sensation in his legs followed by leg weakness which progressed over 8 days. Urge incontinence also developed.

On examination the normal findings were confined to the trunk and legs. He had a spastic hyperreflexic weakness of both legs more marked on the right. Power ranged between 3 and 5/ 5. Clonus was elicited at the right ankle. Abdominal and cremasteric reflexes were absent. Plantar responses were flexor. There was decreased position and vibration sense in the right foot. Pain and temperature sensation were normal. He walked with a wide-based gait. Romberg's sign was positive.

Spinal x-rays and a myelogram were normal. CSF examinations showed a protein concentration of 1,2 g/ℓ, 4 + globulin, 204 lymphocytes mm^{-3} and a Lange colloidal gold curve of 122243221. CSF VDRL was positive to a titre of 1 and CSF Fluorescent Treponema Antibody-Absorption (FTA) test was positive. In the blood VDRL was positive to a titre of 64 and the Treponema pallidum Haemagglutination test (TPHA) was positive.

He was treated with benzyl penicillin G twenty million units daily intravenously for 12 days followed by 10 days of 900,000 units daily of

procaine penicillin intramuscularly. By September 1983 proprioception was normal and power in the legs almost full. No follow-up LP was apparently performed.

Comment

This patient illustrates the development over 1 week of a myelopathy due to meningovascular syphilis affecting the posterolateral portion of the cord, occurring at most 5 months after a primary infection. There was a marked response to treatment.

Case No. 6.

A 20 year old coloured male developed cervical and thoracic backache in September 1979. Ten days later he developed weakness of the legs which rapidly progressed to a complete paraplegia with urinary retention and constipation. He recalled a urethral discharge 3 years previously.

On examination, abnormal signs were confined to the legs. He had a total flaccid areflexic paraplegia with absent abdominal reflexes. There was a sensory level at the 7th thoracic dermatome below which all sensation was absent. Anal tone was flaccid.

Spinal x-rays and a myelogram were normal. CSF examination showed 1 g/l protein, 3 + globulin, 127 neutrophils and 920 lymphocytes mm^{-3}. The CSF VDRL was positive to a titre of 32 and the CSF FTA was positive. In the blood, VDRL was positive to a titre of 64 and TPHA was positive.

He was treated with 20 million units benzyl penicillin G intravenously daily for 2 days followed by 12 days procaine penicillin 1,2 million units daily intramuscularly. No recovery occurred and when last seen in September 1981 he had evolved a spastic hyperreflexic paraplegia.

Comment

This patient illustrates the rapid development of a complete transverse cord lesion following 10 days of backache. In spite of treatment no recovery occurred.

Case No. 7.

A 31 year old previously well coloured female was found to have a VDRL positive to a titre of 8 at an antenatal clinic in November 1979 during her 3rd pregnancy. Apparently no treatment was given. In March 1980 she developed headache and drowsiness. On examination a complete left third cranial nerve palsy was found with mild right hyperreflexia. There was neck stiffness, bilateral fundal haemorrhages and a subhyaloid haemorrhage on the left with papilloedema. Her blood pressure was 170/110 mm Hg.

A CT scan of the head was normal. No LP was performed but a presumptive diagnosis of pre-eclamptic toxaemia with a subarachnoid haemorrhage was made. However 4-vessel angiography was normal. The patient developed pulmonary oedema and transient acute renal failure and emergency caesarian section was performed. The final diagnosis was of a mid-brain infarct.

She was then well until November 1980 when she developed 5 days lower back pain and headache. On examination she had a dilated left pupil and right hyperreflexia. There was marked neck stiffness. An LP showed a protein concentration of 0,8 g/l, 1 + globulin, 190 neutrophils, 9 lymphocytes and 20 red blood cells mm^{-3}. Glucose concentration was normal and no organisms were cultured. A diagnosis of viral meningitis was made and she was discharged.

One week later she developed mild leg weakness and then 2 days later a sudden complete paraplegia with absent sensation and urinary retention. A

further 5 days later she developed a pain in the neck and left arm followed by paralysis of the left arm.

On examination the left pupil was slightly larger than the right and did not react to light but constricted to accomodation. Both arms were weak, the left completely paralysed and areflexic, the right with 3 - 4/5 power and preserved reflexes. There was a complete flaccid areflexic paraplegia with absent abdominal reflexes. There was a sensory level at T_2 dermatone on the right and T_4 on the left below which all sensation was absent.

A repeat LP revealed turbid fluid with protein concentration greater than 4 g/l, 2+ globulin, 33 neutrophils, 99 lymphocytes mm^{-3} and normal glucose concentration. The CSF IgG/albumin ratio was 20%. All cultures were negative. CSF VDRL and FTA were negative. Blood VDRL was positive to a titre of 8 and TPHA was positive. A myelogram revealed a diffuse cord swelling from C_2 to T_9.

Treatment with one million units procaine penicillin intramuscularly daily and dexamethasone was commenced. Intercostal and diaphragmatic weakness developed and she required temporary supportive ventilation. Improvement commenced 8 weeks after treatment started. By 5 weeks (December 1980) she had normal sensation and bladder function, power in the right arm was full, power in the left arm and left leg was grade 4/5 with spasticity and the right leg had grade 2/5 power.

However in January 1981 her left arm and leg again became weak. CSF then showed a protein concentration of 0,4 g/l with 3 lymphocytes $mm.^{-3}$ CSF, VDRL and FTA were negative. Blood VDRL titre was 4 and TPHA remained positive. By March 1981 both legs and the left arm were again completely paralysed with a new sensory level at T_8. A repeat myelogram showed

arachnoiditis from T_{12} upwards with a complete block to the flow of myodil at T_6. The cord was now normal in diameter. CSF taken at the time of the myelogram showed a protein concentration of 0,8 g/l and 8 lymphocytes $mm.^{-3}$ The patient died suddenly in April 1981. No autopsy was performed.

Comment

This patient demonstrates the acute development of a severe myelopathy with a swollen cord similar to that seen on myelography in some patients with pathological findings of acute necrotic myelopathy. She made a remarkable recovery followed by a secondary deterioration related to the development of arachnoiditis, probably secondary to the meningitis rather than to the initial myelogram. In spite of the negative CSF serology the picture was probably that of syphilitic meningomyelitis. The case also demonstrates the possible disastrous consequences of failing to react to positive blood serology.

5.2. Results

5.2.1. General

Five patients were male, 2 female. Six coloured and 1 black. The mean age was 33 years (range 22 : 58). Only 2 patients had previous histories of venereal disease - 1 five months and 1 three years before.

5.2.2. Clinical features

Four patients commenced with backache, 2 with sensory symptoms and 1 with weakness. However, 5 of the 7 developed pain at some stage of the illness and 6 of the 7 sensory signs (only 1 sparing posterior column sensation). There were no Brown-Séquard syndromes. The sensory levels were between T_2 and L_3.

All 7 patients developed leg weakness - 3 with hypertonia and power of 3 to 5/5 and 4 with flaccid areflexic paraplegia ("cord shock"). One patient had arm weakness. Six of the 7 had urinary and 4 faecal symptoms.

As regards the course of the illness, 2 groups were identified. Three patients (e.g. Case No. 5) followed a progressive course over 6 days, 8 days and 7 weeks respectively with a moderate spastic paraparesis on admission. The 2nd group of 4 patients (e.g. Case No. 6) all developed "cord shock". All had a prodromal phase of 6 days to 6 weeks mild weakness (3 of the 4 associated with backache). Then in all 4 patients a second phase of rapidly developing paraplegia occurred over 1 to 5 days.

In all patients but one (Case No 7) the signs were restricted to the spinal cord.

5.2.3. Laboratory Investigations

The blood VDRL was positive in all 7 patients with a titre of 8 - 1024. The TPHA was also positive.

A CSF pleocytosis was found in all patients, ranging from 7-920 cells. Three patients had more than 200 cells. In 5 patients lymphocytes predominated, in 2 neutrophils (54% and 91% respectively). Protein concentration was raised in 6 of the 7 ranging from 0,2 and 4.0 g/l. Only 12 patient exceeded 1,2 g/l. CSF glucose was normal in all patients. CSF VDRL was positive in 5 of the 7 (titres 1-32). Both the patients with negative CSF VDRL had a CSF pleocytosis, had positive blood VDRL (titres 8 and 128) and positive blood TPHA. One of the 2 had a positive CSF FTA test.

Myelograms were normal in 5 patients. In 1 patient it was not performed as the diagnosis was obvious and in 1 (Case No 7) it showed cord swelling.

The ESR ranged between 15 and 114. The white cell count was normal in all patients.

5.2.4. Treatment and outcome

Treatment consisted of procaine penicillin 900 000 to 1,2 million units intramuscularly daily for 10 - 14 days in all patients. This was preceded by a few days intravenous benzyl penicillin G in a dose of 20 million units daily in 3 patients.

Only 1 patient (Case No 5) made a good recovery.[101] Another patient made a fair recovery and a 3rd (Case No 7) improved before secondary deterioration related to arachnoiditis. The other 4 patients did not improve but flaccid paraplegias became spastic with time. Only 2 patients had follow-up lumbar punctures - in both the CSF had returned to normal. There did not appear to be any factors which could predict improvement.

5.3. Additional Cases

Two additional cases with spinal cord neurosyphilis not fulfilling the criteria of this study are now described separately. One of these progressed over 4 years and the other had an extradural mass on myelography.

Case No 8.

A 34 year old previously well coloured male was admitted in May 1981 with a 4 year history of slowly progressive leg weakness and a 6 months history of urgency incontinence. On examination abnormalities were limited to his legs.

He had a spastic hyperreflexic paraparesis with grade 4 - 5 weakness, the left leg being slightly weaker than the right. Plantar reflexes were

extensor. There was patchy loss of pain and touch sensation below the knees and impaired position and vibration sense in the feet.

A myelogram was normal. CSF showed a protein concentration of 0,4 g/l, a trace of globulin, 4 lymphocytes mm^{-3} and a normal glucose concentration. CSF VDRL was positive. The blood VDRL was positive to a titre of 8 and TPHA was positive. Serum folate and vitamin B_{12} concentrations were normal.

He was treated with 2.000 000 units procaine penicillin intramuscularly daily for 3 weeks. There was minimal improvement. Repeat CSF examination in December 1982 showed a protein concentration of 0,2 g/l, a trace of globulin and 10 lymphocytes mm^{-3}. In July 1983 CSF examination showed a protein concentration of 0,2 g/l and no cells. The blood VDRL titre had fallen to 4.

Comment

This patient demonstrates a slowly progressive mainly motor myelopathy over 4 years due to syphilis.

Case No. 9

A 64 year old coloured female with maturity-onset diabetes developed gradual onset of progressive weakness in both legs in June 1984. This was associated with difficulty in micturition.

Abnormal findings were confined to the legs. She had a spastic hyper-reflexic paraparesis with power of grade 3-4/5. Abdominal reflexes were absent. Plantar responses were flexor. Sensation was intact.

Spinal x-rays were normal except for mild degenerative changes. A myelogram showed an incomplete left extradural obstruction of 4 cm at the level of T_4. There was also mild spondolytic cervical cord narrowing. CSF showed protein concentration of 5 g/l, 3 + globulin, 342 lymphocytes mm^{-3}, 7

neutrophils mm^{-3} and normal glucose concentration. CSF VDRL was positive. Blood VDRL was positive to titre of 256 and TPHA was positive.

She was treated with procaine penicillin 1 000 000 units daily intramuscularly for 21 days. There was no neurological improvement. A repeat myelogram 7 weeks later showed the extradural lesion to be definitely smaller. Further CSF and myelographic follow-up is planned.

Comment

This patient probably represents a patient with syphilitic hypertrophic pachymeningitis. She undoubtedly has neurosyphilis and the myelographic picture is suggestive of the extradural inflammatory lesions seen usually in the cervical region.

5.4. Discussion

5.4.1. Clinical picture of spinal cord syphilis

Most of the clinical literature on neurosyphilis predates the use of penicillin. In the last 35 years descriptions of spinal cord syphilis have been restricted to case reports[47,65] usually of 1 patient only and large series of neurosyphilis as a whole[77,98] in which clinical descriptions of individual types are very limited. In spite of the frequent assertion that the pattern of neurosyphilis is changing,[77,102] careful large clinically orientated studies are few.[122]

Neurosyphilis is thought to arise by asymptomatic infection of the meninges early in the course of the disease.[108] In 1 study[116] 11% of patients were shown to have abnormal CSF 3 months after primary infection and 33% by 18 months. In another study[111] 9% of patients with primary syphilis had CSF abnormalities as did 35% with secondary disease.

A. Pre-penicillin studies

The most definitive study of neurosyphilis is the 1946 monograph of Merritt et al[108] and any analysis of more recent data must start with a detailed look at their findings. They classify spinal cord syphilis into 5 groups:

1. Syphilitic meningomyelitis (including such variants as amyotrophic meningomyelitis and syphilitic spastic paraplegia known Erb's paralysis).

2. Spinal vascular syphilis (equivalent to acute transverse syphilitic myelitis).

3. Syphilitic spinal pachymeningitis (including (a) spinal cord gummata and (b) syphilitic hypertrophic pachymeningitis)

4. Syphilitic poliomyelitis.

5. Cord compression by aortic aneurysm or vertebral gumma.

Twenty-nine cases were described. The commonest group was meningomyelitis (15 patients). The basic lesion is chronic inflammation of spinal meninges with inflammatory invasion of the cord parenchyma. Although the authors classify spinal vascular syphilis as a separate group, they admit that in many cases both meningomyelitis and vascular occlusion due to endarteritis play a role. The latent period in this group ranges from a few months to 25 years. In most cases the illness was insidious and progressive rather than acute. Position sense loss occurred in 46% but a spinothalamic sensory level occurred in only 33%. Lower motor neurone signs were seen in the arms in 27% and in the legs in 13%. Associated mental symptoms occurred in 26%; cranial nerve palsies in 13% and abnormal pupils in 46%. Thus isolated spinal cord disease was not common.

The variant of Erb's syphilitic paraplegia refers to cases[160] with a very slow onset and a slowly progressive largely motor paraparesis over a course of years. Erb's original cases did not include any pathology and the condition probably is not a separate clinical entity.[108] Similarly, syphilitic amyotrophy does not usually occur alone but in the form of lower motor neurone signs in a patient with other evidence of cord disease.[108, 160]

Merritt et al's[108] second group of spinal vascular syphilis consisted of 10 patients with sudden onset of complete transverse myelopathy with total distal loss of function. They comment that it is clearly a separable entity, but can complicate cases in the first group. The pathology is cord necrosis due to Heubner's endarteritis of small vessels - lymphocytic and plasma cell infiltration with subintimal fibroblast proliferation.

Four cases of syphilitic spinal pachymeningitis are described - 3 with a localised gumma presenting as a spinal cord tumour and 1 with hypertrophic pachymeningitis. This patient presented with sensory symptoms and lower motor neurone signs in the hands and progressed slowly over 18 months to a spastic paraparesis. Lumbar puncture revealed a picture of spinal block. At autopsy thickened cervical and thoracic meninges (especially dura) were found with infiltration by chronic inflammatory cells and fibroblasts).

Only 1 patient with syphilitic aortic aneurysm compressing the cord was seen and none with vertebral gummata.

CSF protein concentration in the group as a whole ranged from 0,4 - 2,4 g/l (with exception of spinal pachymeningitis when it rose up to 9,2 g/l). Cells ranged from 10 - 360 mm^{-3}. Glucose concentration was usually normal but occasionally low. Merritt et al[108] were prepared to accept negative

CSF Wasserman reactions (WR) (13% - 3 cases) in the presence of positive blood serology. It is not clear whether the 13% all had a CSF pleocytosis.

As regards frequency, spinal cord syphilis was rare in proportion to other forms comprising only 3% of all cases of neurosyphilis studied.[108]

B. Post-penicillin studies

1. Relative frequency

How has the picture of the disease changed? An idea of frequency can be gauged from several series published after 1955. Kofman[98] reported 177 patients with neurosyphilis in 1956. Only 17 had meningovascular syphilis, the number with the spinal form not being specified. Woods (1956)[161] described 24 cases of neurosyphilis in Bantu males of whom 7 had meningo-myelitis and 1 a spinal gumma. However, he notes that his sampling method would have excluded many patients with general paresis and therefore his ratios are inaccurate. Very few clinical details are given.

In 1972 Hooshman et al[77] studied 241 patients with neurosyphilis collected over a remarkably short time of 5 years from the teaching hospitals of 1 United States university. No attempt is made to group the cases conventionally, but it would seem that 9 (4%) may have had cord syndromes.

Luxon et al (1979)[102] described 17 neurosyphilis patients from a London hospital. Of these 2 had definite spinal cord syphilis and 1 had sciatica with myelographic arachnoiditis but no CSF pleocytosis and VDRL positive only in the blood. This is a frequency between 12 and 18%.

Gelfand et al. (1980)[54] described 39 cases in Zimbabwean Africans. He notes that tabes dorsalis is rare and reported 5 cases with satisfactorily documented spinal cord syphilis - a frequency of 12,5%.

A thorough epidemiological study from Denmark[122] found 55 cases of neurosyphilis between 1971 and 1979. Of these, 3 apparently had meningomyelitis (very few clinical details given) and 1 hypertrophic pachymeningitis[3] - a frequency of 7,3%. Over 15 years in Leicester, Alani and Millar[6] reported 1 patient with syphilitic myelopathy in a series of 20 (5%).

From a different view point, Bahemuka[13] found only 1 patient with a syphilitic cause in 23 patients with acute transverse myelopathy in Kenya. Wallace and Cosnett[156] list meningovascular syphilis as a cause of only 1% of all black patients presenting to their Durban hospital with paraplegia.

Thus attempts to reach a conclusion on the relative frequency of spinal syphilis today is hampered by inadequate information and sampling problems. One might well expect the frequency to differ in differing countries. The figures from the countries quoted range between 4 and 18%. In general they are slightly higher than the 3% of Merritt et al.[108] but when a study with good sampling methods is used in a developed country,[122] it is still only 5%. Most studies from hospital departments especially in developing countries will underestimate the incidence of general paresis as these patients are often seen primarily in psychiatric hospitals.

(2) Clinical pattern

There are remarkably few descriptions in the modern literature of the clinical features of spinal syphilis. Fifteen cases of what Merritt et al.[108] would have called meningomyelitis or spinal vascular syphilis can be gleaned from the literature with at least some clinical details given.[47,54,65,86,87,102] It is not possible to separate these 2 groups.

The length of history varies from "sudden onset of paraplegia"[87] to 2 years in 2 patients with concomitant cervical spondylosis on myelography.[86] All but 3 had symptoms under 2 months. Sensory signs are only mentioned in 7 - in 2[102] sensation was normal, in 2 all modalities were affected,[65,87] in 2 proprioception was spared[47,87] and in 1 only vibration sense was affected.[87] Power loss varied from complete paraplegia to mild spasticity only.[87] VDRL was positive in all but 2 cases in whom the CSF FTA was positive.[87] As neither of these 2 had a CSF pleocytosis, the diagnosis is doubtful. Of interest are 2 well documented patients with low CSF glucose concentration compared to blood.[47,65]

Two well documented cases of syphilitic pachymeningitis have been described in the last 30 years. In 1972 Gribble[59] described a patient from Groote Schuur Hospital with a 6 week history of backache and leg weakness resulting in a spastic paraparesis with sensory loss for all modalities. A myelogram showed a concentric compressive extradural lesion at C_7 and C_8. CSF showed a pleocytosis but normal protein concentration and pressure, contrary to the experience of Merritt et al.[108] The blood VDRL was positive but the CSF WR negative. After 3 weeks of treatment a repeat myelogram was normal and the clinical signs had improved markedly. In 1980 Agdal et al.[3] described a patient with a 6 month history of spastic paraparesis who at surgery was found to have a cervical extradural granulomatous inflammatory process. CSF showed a protein concentration of 0,9 g/l, 13 lymphocytes mm^{-3} and a positive VDRL. Woods[161] alludes to 1 patient with 3 gummata found at surgery.

As regards myelographic arachnoiditis, Wadia and Dactur[155] found that syphilis accounted for only 4 of their 70 patients in India and 2 of these

had negative serology. One further case of myelographic arachnoiditis is described by Luxor[102] with minimal signs, positive blood VDRL but negative CSF VDRL and no pleocytosis.

C. Present study

The 9 patients reported here make up one of the largest series with full clinical details since the study of Merritt et al.[108] No attempt has been made to estimate the relative frequency of spinal cord syphilis in the present study as the overall number of neurosyphilis patients in Cape Town seen over the same period is unknown.

In keeping with other studies in the modern literature it is not possible to separate out cases of meningomyelitis from vascular syphilis. Eight of the 9 patients fell within these groups (89%), very similar to the 86% of Merritt et al. These 8 fell into 3 groups - 3 patients followed a slowly progressive course over less than 2 months, 4 patients had a prodromal phase, during which time treatment might have aborted disaster, followed by rapid development of severe paraplegia. This group probably represents an inflammatory process culminating with an acute vascular episode and is the nearest one sees today of Merritt et al's "spinal vascular syphilis". The eighth patient had a slowly progressive course over 4 years with mainly motor involvement. This is a rare presentation, but should be remembered when assessing chronic parapareses. The pathology is probably no different from the rest of the group. Historically it falls under the grouping of Erb's variant.[160]

The ninth patient probably had syphilitic pachymeningitis in the thoracic region. Merritt et al's case had cervical and thoracic dural

inflammation, whereas the other 2 patients described above[3,59] had cervical inflammation only. One of these 2 and the present patient were diagnosed myelographically. CSF protein concentration was markedly raised. If such a lesion is seen and the CSF serology is positive, a course of treatment should be given and the myelogram repeated before surgical intervention is considered.

One of our patients developed secondary arachnoiditis. The role of syphilis in the pathogenesis of myelographic arachnoiditis is uncertain - it is definitely very uncommon and other diagnoses should be considered first. Myelogram in syphilitic meningomyelitis is usually normal.

Seven of the 9 patients had sensory loss and of these only 1 spared position sense. This should be compared to 50% of the idiopathic group who showed sensory dissociation. Syphilis seems to have a predeliction for posterior column damage - tabes dorsalis is another example of this.

All except the patient who progressed over 4 years had raised CSF cell counts. While the majority had lymphocytic predominance, 2 of the 8 (25%) had initially more neutrophils. This does not exclude the diagnosis. Similarly 2 of the 9 patients had normal CSF protein concentration (22%). All the patients in the present series had normal CSF glucose concentrations, but 3 of the patients in the recent literature[47,59,65] (1 with pachymeningitis) had CSF glucose about 1/3rd of blood glucose concentration. No patient had extremely low levels.

5.4.2. Laboratory criteria for diagnosis

No authoritative criteria for the diagnosis of neurosyphilis have ever been laid down. Merritt et al[108] included patients with negative CSF

serology and no pleocytosis. With the development of specific anti-treponemal antibody tests such as FTA,[83] the picture has become confused.

As regards blood tests, the nonspecific reaginic antibody tests such as VDRL are said to be less sensitive for tertiary syphilis than specific tests. Holmes,[75] quoting data from the USA Centre for Disease Control, maintains that 13% of patients with tertiary syphilis are VDRL negative but FTA positive. However my personal experience is that in meningovascular syphilis as opposed to general paresis or tabes dorsalis, a negative blood VDRL but positive TPHA or FTA is exceptionally rare. In the present series all 9 patients had a positive blood VDRL. As discussed earlier, 2 patients with idiopathic myelopathy had negative blood VDRL but positive TPHA. In both the CSF VDRL was negative and both improved without penicillin. It is accepted today that in spite of higher sensitivity for primary and some forms of tertiary syphilis, the FTA should not be used as a screening test because of it expense and its technical difficulty leading to reduced reliability in unskilled hands.[31,83]

In the CSF three problems arise. Firstly, what is the significance of a positive CSF VDRL with a normal cell count? A positive CSF VDRL is considered by some[48] virtually diagnostic of neurosyphilis if there has been no obvious blood contamination of the specimen. Other authors insist on a pleocytosis[161] or in absence of an initial pleocytosis, either obvious clinical improvement with therapy or the development of a pleocytosis with treatment.[77] It would appear that while the presence of increased cells in the CSF is not essential it is at least desirable.

Secondly, what is the role of CSF FTA? Some authors[42,77,87] have advocated its use in place of the CSF VDRL and there is 1 report[150] of

Treponema pallidum isolated from CSF in the presence of a positive CSF FTA but negative CSF VDRL and normal cell count. Considerable doubts however have developed. Apart from the difficulty and expense of the test, there is some evidence that CSF specific antibodies depend on the presence of circulatory immunoglobulin derived from the serum.[48] Two studies[84,151] have shown that the CSF FTA titre is significantly lower than the same titre in the blood, supporting the possibility of antibody diffusion. Whether this would imply some blood-brain barrier breakdown is uncertain. However 1 study[33] has shown that as little as 0,005 μl serum or 42 red blood cells mm^{-3} contamination of CSF with the patient's own blood at LP is sufficient to convert a negative CSF FTA to positive. Far more blood is needed to convert a CSF VDRL. Thus the consensus today seems to be that the FTA test should not be used in the CSF as a diagnostic criterion for neurosyphilis.[48]

Thirdly, what is the significance of a positive serum VDRL but a negative CSF VDRL? Almost all series accept a certain percentage of patients in this group as having neurosyphilis. Merritt et al[108] for instance, noted 28% of their tabetics, 12.5% of their patients with cerebral meningovascular syphilis and 13% with spinal meningovascular syphilis had negative CSF WR's. It can of course be argued that some of these patients did not in fact have neurosyphilis, but the fact remains that authors with experience of the clinical and pathological features were prepared to accept the diagnosis. Most subsequent authors followed this lead[48,77] while a very few have insisted on the stricter criterion of a positive CSF WR.[161] There can be no definite answer to this problem as the absolute diagnostic standard is pathology which today is rarely available. Merrit et al unfortunately did not include among their many case histories any patients with negative CSF WR

and autopsy confirmation of the diagnosis. However the acceptance of patients with negative CSF VDRL as having neurosyphilis if the clinical condition is compatible, blood serology is positive and there is a CSF pleocytosis falls within the realm of reasonable clinical practice.

With this background, I suggest the following laboratory criteria for the diagnosis of meningovascular syphilis in an appropriate clinical setting:

1. Definite neurosyphilis.

(a) Blood non-specific (VDRL) and specific (TPHA or FTA) test positive.

(b) CSF VDRL positive and a CSF pleocytosis.

2. Probable neurosyphilis.

(a) Blood non-specific (VDRL) and specific (TPHA or FTA) test positive.

(b) Either CSF VDRL negative but CSF pleocytosis present

or

CSF VDRL positive but normal CSF cell count.

3. Possible neurosyphilis.

(a) Blood non-specific (VDRL) test negative but specific (TPHA or FTA) test positive.

(b) CSF pleocytosis.

If the CSF is entirely normal with respect to cells and serology, extreme caution should be exercised in diagnosing meningovascular syphilis. (These criteria do not apply to parenchymatous neurosyphilis, especially tabes dorsalis, where fewer positive tests are required in the correct clinical setting).

In the present series 7 of the 9 patients fulfilled the criteria for definite neurosyphilis and 2 the criteria for probable neurosyphilis. Of the

4 patients classified as idiopathic myelopathy with positive blood serology (see earlier), only 1 fulfilled even the criteria for possible neurosyphilis and none for probable or definite neurosyphilis.

5.4.3. Therapy

The recommendations of the Centre for Disease Control at Atlanta, Georgia for the management of neurosyphilis[136] are either benzathine penicilin G, 7,2 million units intramuscularly in 3 divided doses for 3 successive weeks or aqueous procaine penicillin G, 9,0 million units intramuscularly in 15 daily doses of 600 000 units each.

However there are reports of clinical failure with benzathine penicillin[57] and of re-culture of the organism from the CSF after its administration.[150] A number of small studies have shown consistently that CSF penicillin concentrations are below the commonly accepted treponemacidal level after benzathine penicillin therapy.[38,113,125] Similarly, procaine penicillin G 600 000 units intramuscularly failed to provide adequate CSF concentration in 2 studies (a total of 5 patients).[39,163] When combined with probenecid, procaine penicillin appears to achieve higher CSF concentrations.[39,40] Intravenous aqueous pencillin G in doses of 10-twenty million units daily achieves consistently CSF concentrations far in excess of the minimum acceptable level.[125,136,163]

Apart from the small numbers of patients, the problem with most of these studies is that the CSF concentrations are being measured in patients who do not have neurosyphilis. Thus the question whether lower doses of penicillin may be adequate in a setting of meningeal inflammation and disturbed blood-brain barrier function, remains unsettled. In addition the commonly accepted

minimum treponemacidal penicillin concentration is extrapolated from serum concentrations and may well be higher than required.[81]

In summary present evidence suggests that benzathine penicilin G is probably inadequate for neurosyphilis and aqueous penicillin G intravenously is certainly acceptable. The role of procaine penicillin G is not adequately delineated although anecdotal clinical observations suggest that it is effective.

The patients in this study were treated with procaine penicillin for 10 to 14 days. Three also received intravenous aqueous penicillin G for a few days. Unfortunately adequate CSF follow-up was not performed. It must be emphasized that the CSF should be re-examined 6 months after therapy. A normal or markedly reduced CSF white cell count is probably the best laboratory indicator of treatment effectiveness.[76]

5.4.4. Conclusions

1. From a review of the literature, there is no clear evidence that the percentage of cases of neurosyphilis affecting the spinal cord has significantly altered since the use of penicillin.

2. The present study suggests that the old classification of spinal syphilis is still valid except that it is not possible to differentiate between meningeal and vascular pathogeneses.

3. The vast majority of patients with spinal cord syphilis have the meningovascular form of the disease but hypertrophic pacchymeningitis also occurs. Spinal cord gummata are exceptionally rare.

4. The meningovascular group progress slowly over a number of weeks and

some are complicated by superimposed acute severe paraplegia. This latter event presumably represents vascular occlusion. Slow progression over years is exceptionally rare but does occur.

5. The majority of patients with spinal cord syphilis have impaired position sense suggesting that syphilis has a predilection for the posterior columns.

6. The majority of patients will have a raised CSF protein concentration and pleocytosis which is usually lymphocytic but may rarely be neutrophilic. The CSF glucose concentration is normal in the majority of the patients but can be moderately low.

7. Laboratory criteria for the diagnosis of meningovascular syphilis have been proposed, with 3 categories of differing probabilities.

8. The majority of patients do not improve significantly even with adequate treatment, but good recoveries occasionally occur and intensive therapy should therefore always be administered.

9. A literature review suggests that benzathine penicillin G is probably inadequate for the treatment of neurosyphilis and that intravenous benzyl penicillin G is undoubtedly effective. Inadequate information is available to assess procaine penicillin G intramuscularly but anecdotal evidence suggests its possible effectiveness.

6. MYELOPATHY ASSOCIATED WITH PULMONARY TUBERCULOSIS

6.1. Case reports

Four patients developed myelopathy in association with pulmonary tuberculosis (PTB) in the absence of tuberculous meningitis or vertebral tuberculosis. In view of the rarity of this condition, all 4 patients are described fully.

Case No. 10

A previously well 28 year old coloured female developed malaise, cough, loss of weight and night sweats in December 1983. A few weeks later she noticed progressive loss of vision in her left eye culminating in complete blindness by the end of January 1984. Thereafter vision began deteriorating in her left eye. On 7 February 1984 she was admitted to a peripheral hospital where a chest x-ray showed right upper lobe consolidation and a Ziel-Niehlsen stain of her sputum showed acid-fast baccili (AFB's). She was treated with streptomycin 1 g daily intramuscularly, pyrazinamide 2 g daily, isoniazid 400 mg daily and rifampicin 450 mg daily orally.

On 13 February she developed weakness in her right leg. CSF examination the next day showed a protein concentration of 0,5 g/l, 2 lymphocytes mm^{-3} and normal glucose concentration. No AFB's were seen. Prednisone 60 mg was commenced. Over the next 2 weeks the weakness in the right leg progressed to complete paralysis. Two days before transfer to Groote Schuur Hospital, weakness developed in the left leg with loss of sensation in both legs. This was associated with urinary retention, faecal incontinence and high thoracic backache.

On admission to Groote Schuur Hospital on 2 March she was apyrexial but tachypnoeic with coarse crackles audible in the right upper lobe. She was fully conscious and orientated. The pupils were dilated - the left was fixed and the right barely reactive to light. There was no perception of light in the left eye and only hand movements perceived on the right. Both optic discs were atrophic.

The fifth and sixth thoracic spinous processes were extremely tender. There was a sensory level at T_6 below which all sensory modalities were absent bilaterally. Abdominal reflexes were absent. There was a complete hypotonic areflexic paraplegia with extensor plantar reflexes. The anus was flaccid and a urinary catheter was in place.

CSF examinations on admission showed a protein concentration of 0,2 g/l, no globulin and no cells. AFB's were not seen and culture for TB bacilli was negative. Non-specific CSF tests for syphilis were negative. Spinal x-rays and a myelogram were normal as was an isotope bone scan. All serum immunological tests for auto-immune and infective disease were negative. The blood leucocyte count was 14,8 x $10^9/\ell$ and the ESR was 87. A chest x-ray showed extensive active tuberculous changes in the right upper lobe and the left middle and lower lobes.

Anti-tuberculosis therapy and prednisone were continued. Her course was complicated by severe mid-thoracic backache with pain radiating anteriorly bilaterally. She lost sensation in the fingers of both hands and developed weakness of grip bilaterally. The thoracic sensory level remained constant as did her visual acuity. No recovery occurred in her legs. She was transferred on 18 April 1984 to a peripheral TB hospital where she died. The cause of death is unknown as no autopsy was performed.

Comment

This patient illustrates the development of bilateral optic neuropathy at the time of the onset of symptoms of PTB and prior to the administration of therapy. An acute myelopathy commenced 1 week after therapy started and CSF examination then showed only a minimally raised protein. There was no evidence of TB meningitis and a myelogram was normal. Of note was the severe backache with radiation.

Case No 11.

A previously well 20 year old coloured female developed PTB in December 1982. She received a 6 month course of therapy with symptomatic recovery. In December 1983 she developed loss of weight, night sweats and haemoptysis. In late February 1984 she developed thoracic backache radiating anteriorly as a bilateral burning band. Two days later she developed bilateral leg weakness, worse on the left and bilateral leg numbness. She developed painful urinary retention needing catheterisation, but this resolved in 24 hours. The leg weakness reached a maximum in 2 days at which stage she could still walk.

About the middle of March 1984 she developed decreased vision in the lateral half of each visual field associated with retro-orbital pain. Ophthalmological examination then revealed a bitemporal hemianopia. Two days later she was admitted to a tuberculosis hospital where chest x-rays showed patchy opacification in the right lung and sputum was positive for AFB's. treatment was commenced with streptomycin 1 g daily, isoniazid 400 mg daily, rifampicin 450 mg daily and pyrazinamide 2 g daily.

Over the next month her leg weakness improved but the severe radicular

pain remained. Her eyesight, however, continued to deteriorate to complete bilateral blindness. One month after therapy commenced, her legs again weakened reaching a maximum over 6 days. She was transferred to Groote Schuur Hospital on 19 April 1984.

On examination she was apyrexial and undistressed. Chest examination was normal. She was fully conscious and alert. Both pupils were fully dilated and reacted only sluggishly to light, the left more than the right. There was no perception of light in the right eye and acuity in the left was limited to light perception only. Fundi were normal. The remaining cranial nerves and the arms were intact. There was increased tone in both legs with appropriate hyperreflexia and bilateral extensor plantar responses. Power was grade 3-5/5 on the right and 1-2/5 on the left. There was a sensory level at T_6 below which touch, pain, temperature and vibration sense were impaired. Position sense was intact.

Spinal x-rays and a myelogram were normal. A CT scan of brain and pituitary fossa was normal. CSF examination on admission showed a protein concentration of 0,2 g/l, no globulin, no cells and normal glucose concentration. AFB's were not seen and culture for TB bacilli was negative. All serum immunological tests for infective or auto-immune disease were negative. The blood leucocyte count was $8,0 \times 10^{-9}/\ell$ and the ESR 87.

Prednisone was commenced and her anti-TB therapy continued. By 15 June the power in her right leg had returned to normal and the left improved to grade 4 - 5/5. Both legs remained spastic. The sensory level fell to L_1. However her severe root pain at T_6 persisted, relieved eventually by combination of amitryptiline and phenytoin. Her vision did not improve and when last seen on 27 July she had developed bilateral optic atrophy.

Comment

This patient developed the first episode of a biphasic myelopathy and retrobulbar optic neuropathy some months after the onset of symptoms of PTB, prior to commencement of therapy. There was no evidence of TB meningitis and a myelogram and CT scan were normal. Of note was the biphasic course of myelopathy with some recovery, the optic neuropathy presenting as a bilateral hemianopia and again the severity of the root pain.

Case No. 12

A 32 year old previously healthy coloured female developed abrupt loss of vision in the left eye associated with retro-orbital pain in May 1977. Vision slowly returned over 3 days. Over the next 2 months she noticed loss of weight but no cough. On 25 June she developed bilateral retro-orbital pain associated with vomiting and the rapid loss of vision in both eyes. She was admitted to Groote Schuur Hospital on 1 July.

On examination she was pyrexial and wasted. Coarse crackles were audible in the left upper lobe. Higher mental functions were normal. The pupils were fixed and dilated and fundoscopy showed bilateral optic atrophy. There was no perception of light in either eye.

Chest x-ray showed consolidation and cavitation in the left lingula and AFB's were seen in the sputum. CSF examination showed a protein concentration of 0,3 g/l, no globulin, 3 lymphocytes mm^{-3}, normal glucose concentration and negative serologic tests for syphilis. No AFB's were seen or cultured. A CT scan of the head was normal. She was discharged on treatment with streptomycin, isoniazid, ethionamide, rifampicin and pyrazinamide.

On 27 July she developed thoracic backache radiating down the right leg. Over a few days she developed progressive weakness in both legs.

On examination on 30 July her eye signs remained unchanged. The remainder of the cranial nerves and the arms were normal. She had a complete areflexic paraplegia with intermittent flexor spasm and bilateral extensor plantars. There was a sensory level at T_6 below which touch, pain and temperature were reduced bilaterally. Vibration and position sense were impaired in the left foot only. She had urinary retention and a distended bladder.

Spinal x-rays and a myelogram were normal. Repeat CSF on 30 July showed a protein concentration of 0,4 g/1, no globulin, no cells and normal glucose concentration. The CSF IgG - albumin ratio was normal. Again bacterial studies were normal. All serum immunological tests were normal.

Anti-TB therapy was continued but no steroids used. Her weakness improved and by 17 August she had grade 3-4/5 power in the legs. When last seen at the end of 1977 she was able to walk with much spasicity and had recovered bladder control. Her blindness persisted.

Comment

This patient developed a bilateral optic neuropathy concomitantly with PTB. She developed a myelopathy a few weeks after commencement of treatment. There was no evidence of TB meningitis and a myelogram and CT scan were normal. The myelopathy partially recovered but the blindness remained.

Case No 13.

A 41 year old black women had a 15 year history of intermittent pulmonary tuberculosis. In June of 1979 she was again found to have AFB's in her sputum and therapy with isoniazid, pyrazinamide and ethambutol was

recommenced. In December 1979 she developed paraesthesiae in her feet and weakness in her legs. The weakness progressed for 1 month and then remained static.

On examination 8 months later when she was first seen she had normal higher functions and cranial nerves. Tone and power were normal in her arms but the reflexes were symmetrically brisk with bilateral positive Hoffman's signs. There was a hypertonic hyperreflexic paraparesis with extensor plantar responses. Power in the legs ranged between 2 and 4/5. There was decreased touch and vibration sense in the feet.

Spinal X-rays and a myelogram were normal. CSF on admission showed a protein concentration of 0,3 g/l, no globulin, 6 lymphocytes mm^{-3} and normal glucose concentration. No AFB's were seen or cultured. Serological tests for syphilis were negative. The ESR was 120. A chest X-ray showed extensive bronchiectasis with bullous formation.

Anti-TB treatment was continued. Her neurological condition remained static until her death in February 1984 from cor pulmonale. No autopsy was performed.

Comment

This patient developed a static mild spastic paraparesis while on treatment for PTB. There was no evidence of tuberculosis meningitis and myelography was normal.

6.2. Results

All 4 patients were female, 3 coloured and 1 black. The average age was 26,5 years (range 18-32).

Three of the 4 patients had neuromyelitis optica (Devic's syndrome) and 1 had myelopathy alone. Two of the 3 patients with Devic's syndrome

commenced with optic neuropathy and 1 with myelopathy. All 3 of these patients had some neurological involvement before treatment was commenced. Two had already optic neuropathy and developed myelopathy while on treatment (1 week and 3 weeks after treatment commenced). The third patient developed both optic neuropathy and myelopathy before she received any treatment. The fourth patient with myelopathy alone had been on treatment for 6 months when her paresis commenced.

One patient (case No 10) developed "spinal shock" and followed an ascending course with arm involvement. She died at a peripheral hospital probably from an ascending myelopathy. The other 2 patients with Devic's syndrome showed marked improvement in their myelopathy symptoms. One of these followed a biphasic course with improvement and relapse. The fourth patient developed a mild static myelopathy alone. In all 3 patients with Devic's syndrome no recovery from visual loss occurred.

A marked feature in the first 2 patients was the severity of the back-ache and root pain far out of proportion to the pain experienced by any other patient in this series. So severe was their pain that repeated investigations for other pulmonary or abdominal pathology were performed with negative results. At times opioid analgesics were neeeded and transcutaneous nerve stimulation was used with limited results.

CSF of all 4 patients was normal except for a marginal rise in protein concentration (0,5 g/l in case No 10) and cell count (6 lymphocytes mm^{-3} in cases No 10 and 13).

Steroids were used in the first 2 patients but their effect is uncertain.

6.3. Discussion

6.3.1. Clinical features

Only 5 previous patients with neuromyelitis optica and PTB have been described as well as 6 others with myelopathy alone.

A. Neuromyelitis Optica

In 1956 Dickson et al[34] described a patient with PTB who 1 month after commencing treatment with streptomycin and isoniazid developed bilateral optic neuropathy. It is of interest that the patient's visual symptoms commenced, as in one of the present series, with a bitemporal hemianopia and progressed to complete blindness. Treatment was stopped for 2 weeks and then restarted. One month later he developed a severe flaccid paralegia with T_8 sensory level and died. Autopsy showed demyelination of the superomedial portion of the optic tract and extensive cord necrosis but no evidence of TB in the nervous system. The medial distribution of the optic tract myelination may explain the initial hemianopia. The authors considered the illness to be due to isoniazid toxicity.

Soteres et al[142] described a similar patient on treatment with isoniazid who developed a severe myelopathy and then 4 weeks later a left optic neuropathy. The patient died and at autopsy marked optic nerve demyelination and extensive spinal cord necrosis, with at places inflammatory cell infiltrates, was found. Again there was no evidence of nervous system TB. Again isoniazid was considered the most likely cause.

The patient of Tommasi et al[149] developed bilateral retrobulbar neuropathy before treatment for PTB was commenced and 2 weeks later developed a tetraparesis and died. Again pathology was that of inflammatory demyelination of optic nerves and cord.

The condition was first discussed comprehensively by Hughes and Mair[80] who reported 1 further case. Two months after commencing treatment with rifampicin, isoniazid and ethambutol, the patient developed bilateral optic neuropathy (commencing with an homonymous hemianopia) and then 1 month later an ascending myelopathy from which he died. All drugs had been stopped after visual loss developed. Of note is the severity of the backache described, similar to that of 2 of the patients in the present series. Pathology was that of demyelination of the optic chiasms, optic nerves and tract and severe necrosis of the cord.

Barbizet et al[15] described a patient who developed acute myelopathy and one month later a unilateral optic neuropathy. She was found to have PTB. After treatment commenced the myelopathy progressed to a quadriplegia and optic neuropathy developed in the other eye. The myelopathy recovered well and by 1 year she was left with a spastic paraparesis. Vision did not recover.

Thus 3 of the 5 patients were on treatment when neurological symptoms started. Three commenced with optic neuropathy and 2 with myelopathy. This is similar to the cases in this series and similar to the studies of idiopathic Devic's syndrome, where an equal number of cases commenced with myelopathy and optic neuropathy.[23] Including the 3 in the present series, 6 of the 8 patients (75%) were female. Five of the 8 patients died (63%).

B. Myelopathy alone

Money (1960)[114] described 3 cases of myelopathy alone in Nigerian blacks on isoniazid. The first patient apparently did not have active TB and developed a slowly progressive purely motor myelopathy over 9 months. This

improved once isoniazid was stopped. The second and third patients both with PTB and treated with isoniazid developed similar spastic parapareses with apparently later improvement. One of these patients also had visual impairment but no further details are given. The author ascribed the symptoms to isoniazid toxicity. Unfortunately inadequate documentation and lack of investigation (no myelograms were performed) makes further evaluation difficult.

Hughes and Mair[80] described 2 additional fatal cases of myelopathy alone. The first patient had not yet commenced treatment for PTB. His myelopathy partially remitted but 2 months later he developed a severe quadriparesis and died. The second patient had commenced treatment 5 days before neurological symptoms started. Pathology in both cases showed extensive cord demyelination.

Reid and Bone (1980)[130] described a patient with spastic paraparesis with sensory level which developed 5 months after commencing treatment for PTB with ethambutol, with rifampicin, isoniazid and pyrazinamide. CSF was normal except for protein concentration of 0,6 g/l and a myelogram was normal. Gradual improvement occurred.

6.3.2. Differential diagnosis

The commonest cause of myelopathy in the setting of PTB is Pott's disease of the spine. Other rarer possibilities are epidural, intradural extramedullary or intramedullary tuberculomata and arachnoiditis with endarteritis.[97] The patients reported here all had normal spinal x-rays, normal myelograms and essentially normal CSF examinations.

The commonest cause of optic neuropathy in this illness is TB

arachnoiditis with or without endarteritis affecting the optic nerve. Alternatively basal meningitis may result in hydrocephalus causing secondary visual impairment.[115] The patients in this study had normal CT scans and the essentially normal CSF findings virtually excluded active basal arachnoiditis.

6.3.3. Pathogenesis

(a) Role of tuberculosis

In view of how common TB is in South Africa, it must be asked whether the relationship of the syndrome to TB is purely coincidental. However although TB is common, Devic's syndrome is rare in Cape Town.[8] In the 7½ years covered by this study, only 4 cases were identified and 3 were in the setting of pulmonary TB. (Devic's syndrome appears slightly commoner in the blacks of Natal. Cosnett[27] recorded 5 patients in a 2000 bed teaching hospital over a 2½ year period. One was found to have tuberculous adenitis some years after the Devic's syndrome commenced).

In about 1/3 of cases of Devic's syndrome unassociated with PTB reported in the literature a non-specific viral type illness preceded the neurological symptoms.[23] The syndrome has been reported following varicella[21] and measles infection.[110] Thus precedence exists for its occurrence in the setting of TB. The reported occurrence of Guillain-Barré syndrome in patients with TB [154] is further indirect evidence that nervous system demyelination can follow tuberculous infection.

The cord pathology in the cases described is similar to that of idiopathic myelopathy, ranging from extensive cord necrosis with little inflammation to a predominantly demyelinating process with inflammatory infiltrate. Certainly two of our patients and the patients of Reid and

Bone[130] and Barbizet et al[15] improved markedly suggesting a partially reversible lesion.

Hughes and Mair[80] suggest that the pathogenesis is a hypersensitivity reaction to a myelin antigen. The tuberculous infection may have an adjuvant effect, non-specifically amplifying a response to minor myelin damage. Alternatively the TB bacillus may share antigens with myelin proteins or possibly mycobacteria or their degradation products might lodge in the cord eliciting an immune response resulting in "innocent bystander" demyelination.

(b) Role of drugs

Originally both the optic neuropathy and myelopathy were thought to be due to isoniazid therapy. Isoniazid certainly can cause peripheral neuropathy and encephalopathy.[91] It has been considered to cause optic neuropathy[4,92] but only a few cases have been reported despite widespread use of the drug and the relationship is not well documented. Myelopathy has resulted from administering massive doses of isoniazid to monkeys,[132] but clinical cases are not easily provable.

At least 2 cases in the literature[15,149] developed the onset of Devic's syndrome before treatment was instituted and another patient[80] progressed from optic neuropathy to myelopathy after drugs had been stopped. The patients in the present series provide further evidence against the role of drugs- all three patients with Devic's syndrome developed the onset of neurological symptoms before drugs were commenced and in one both myelopathy and optic neuropathy antedated their use.

Thus in summary, drugs probably play little role in the pathogenesis of the illness and should not be discontinued if Devic's syndrome develops.

6.3.4. Conclusions

1. Although PTB is extremely common in South Africa, the rarity of Devic's syndrome suggests that a relationship exists between the two conditions.

2. The syndrome may commence either with myelopathy or optic neuropathy.

3. Severe back pain and radicular pain are common.

4. The syndrome appears to be commoner in women.

5. The prognosis for the myelopathy is variable - in most patients it takes a fulminating form of progressive cord necrosis while in some it follows a milder course wth improvement and sometimes a remission and relapse. The prognosis for the optic neuropathy is very poor and the mortality rate for the group as a whole is high.

6. The pathogenesis may well be a hypersensitivity reaction involving mycobacterium tuberculosis and is unlikely to be related to isoniazid.

7. Myelopathy alone also occurs with PTB. While it is probably due to the same factors, too few cases are reported to be sure of its relationship to TB.

7. MYELOPATHY ASSOCIATED WITH OTHER SPECIFIC INFECTIONS.

7.1 Mycoplasma pneumoniae associated myelopathy

There was only 1 patient in this group.

7.1.1. Case Report (Case no 14)

A previously well 32 year old white male developed fever and a cough. Seven days later he noticed he had become jaundiced. After a further 3 days he developed leg weakness and within 24 hours had become densely paraplegic.

On examination, he was pyrexial with signs of consolidation over the left lower chest. Higher mental function and cranial nerves were normal. There was mild weakness (grade 4-5) in the arms but a complete flaccid areflexic paraplegia with a sensory level at T_4 below which all sensory modalities were absent. He had urinary retention needing catheterisation and faecal incontinence.

Chest x-ray showed a left lower lobe pneumonia. A myelogram was normal. CSF showed a protein concentration of 0,5 g/l, a trace of globulin, 55 neutrophils and 49 lymphocytes $mm.^{-3}$ All stains and cultures for organisms were negative as was syphilitic serology. There was biochemical evidence of a mild hepatitis. The haemoglobin concentration was 10 g/l with a corrected reticulocyte count of 6%. The blood leucocyte and platelet counts were normal. The direct Coomb's test was positive. Mycoplasma titres in the serum were 1280 the day after admission (12 days after onset) and 320 two weeks later. The rheumatoid factor and antinuclear factor were absent, but circulating immune complexes were raised at 15,6% (normal 0 - 7%).

The patient was managed by intubation and supportive ventilation. He was treated with a number of antibiotics including tetracycline. On the 9th

hospital day he was weaned from the ventilator. About 1 week later he had a single generalised seizure. A CT scan was normal and an electro-encephalogram showed bilateral slowing. A repeat CSF examination showed a protein concentration of 0,5 g/l and 4 lymphocytes.mm^{-3}

He slowly improved neurologically and 3 months after onset of symptoms had begun walking with assistance. Follow-up three years later showed fair recovery. His arms were normal. There was a sensory level at T_{11} below which all modalities were reduced. Both legs were spastic with 4/5 power and he was able to walk with crutches. He complained of urgency incontinence.

7.1.2. Discussion

Mycoplasma pneumoniae was first isolated in 1962.[159] Many years earlier, it was recongised that some patients with primary atypical pneumonia had neurological complications.[143,153] Yesnick in 1956[162] reviewed the literature and found 38 patients with neurological manifestations of whom 9 had cord lesions. However, in the absence of specific immunological tests, diagnosis was purely clinical and may have been inaccurate in many cases.

However, since the development of easily performable complement fixation test, diagnosis has been simpler. A titre of greater than 128 is considered suggestive of recent infection,[146] though obviously a four-fold rise in titre is preferable.[24] However the antibodies peak early at 3 to 4 weeks[146] and a four-fold fall in titre, as in the patient in the present series, can also be significant.[159]

Neurological complications well documented in the last 20 years include meningitis, meningo-encephalitis, acute polyradiculoneuropathy[72] and transverse myelopathy.[159] Less than 10 patients with acute myelopathy

have been documented over this period.[28,96,103,118,159] In all these patients the myelopathy developed in a setting of pneumonia, but patients with meningitis and Guillain-Barré syndrome have been described[72] with raised mycoplasma antibodies but minimal extraneural manifestations. Recently doubt has been expressed[24] about accepting such pure neurological syndromes as due to mycoplasma because of the commoness of mycoplasma infection in the population. It has been estimated that 2 Mycoplasma pneumonias occur per 1000 population per year and 30 mycoplasmal upper respiratory tract infection occur for each case of pneumonia. Thus the possibility of isolated neurological illness being due to Mycoplasma pneumoniae remains unsettled.

The neurological features do not differ from idiopathic acute myelopathy.[159] Prognosis is variable, ranging from complete recovery[159] to permanent disability.[96] The patient reported in the present series made a fair recovery. Often intracranial manifestations can accompany the myelopathy.[162] The present patient had one seizure during recuperation.

CSF shows a raised protein concentration with a pleocytosis either with predominantly lymphocytes[118,159] or neutrophils.[96] Two patients had low CSF glucose concentrations.[96,103] An associated laboratory finding of help is an auto-immune haemolytic anaemia with cold agglutinins.[146] The present patient showed haemolysis with a positive Coomb's test. Unfortunately tests for cold agglutinins were not performed.

Apart from 1 case, mycoplasmas have not been isolated from the CSF or nervous tissue.[103] There is some experimental evidence for a neurotoxin being produced by other mycoplasmas but toxins from Mycoplasma pneumoniae have never been demonstrated.[24] The haemolytic anaemia is due to

immunological cross-reactivity between the red blood cell I antigen and a mycoplasma glycolipid. It has been postulated that the neurological complications may be due to similar cross reactivity with nervous tissue.[24] With such a pathogenesis in mind, plasmapharesis has been attempted in 1 patient with mycoplasma related myelopathy with unconvincing results.[28]

7.2. Epstein-Barr virus related myelopathy

7.2.1. Results

I have elsewhere reported the 2 patients with Epstein-Barr virus related myelopathies.[138]

The first patient developed typical infectious mononucleosis with a rash, adenopathy and palatal petechiae complicated by an acute myelopathy in association with a cranio-spinal polyneuropathy. The evidence for the myelopathy was a clear truncal sensory level with early painless sphincter involvement. However in addition the patient developed areflexic weakness of the arms and bulbar and facial paralysis with bilateral sixth cranial nerve palsies. Nerve conduction studies showed severe slowing of motor conduction confirming a demyelinating peripheral neuropathy.

The Paul-Bunnell test was strongly positive with a rising titre. CSF examination showed a protein concentration of 0,6 g/l, no globulin, 8 lymphocytes, 1 neutrophil mm^{-3} and a normal glucose concentration. One week later repeat CSF showed a protein concentration of >2 g/l, 4+globulin 16 lymphocytes and 7 neutrophils $mm.^{-3}$ Recovery was fair and 6 months after the illness he was able to walk without assistance.

The second patient developed lumbar backache followed by weakness of the legs and urinary retention with a clear truncal sensory level for pain and

touch. The only manifestation of extra-neurological disease was the development of enlarged submandibular lymph nodes.

The Paul-Bunnel test was negative, but antibodies to the D-component of Epstein-Barr virus early antigen were present to a titre of greater than 20. All other screens for viral agents including cytomegalovirus and hepatits B virus were negative. CSF examination showed a protein concentration of 0,1 g/l, no globulin, 1 lymphocyte mm^{-3} and a normal glucose concentration. Recovery commenced after 2 days and by 10 days the only residual deficit was trunk weakness and a persistent sensory level.

7.2.2. Discussion

Between 1% and 2% of patients with infectious mononucleosis develop neurological complications.[17] Minor disturbances such as headaches and mild meningitis may be commoner, as may abnormal electroencephalograms.[53]

Neurological manifestations can be classified as aseptic meningitis (meningo-encephalitis), polyneuropathy (including Guillain-Barré Syndrome), mononeuropathy, monoradiculopathy and acute myelopathy. The encelphalitis can result in disturbances of consciousness from confusion to coma, seizures and focal disturbances including hemiplegia, chorea and brain-stem and cerebellar disorders.[53] Mononeuropathy of all 12 cranial nerves as well as the spinal nerves has been described.[134]

Acute myelopathy is one of the rarest neurological complications of Epstein-Barr virus infections, with fewer than 20 cases in the literature.[29,43,61,117] In many cases the myelopathy is associated with a meningo-encephalitis but can occur in isolation.[29] In the first of the 2 patients reported here it occurred with a demyelinating peripheral

neuropathy. The clinical picture does not differ from idiopathic acute myelopathy. The CSF usually shows a pleocytosis with raised protein concentration,[61] but may show raised protein alone[29] or be normal, as in one of the 2 present cases.[138]

Although the neurological complications usually follow the classic illness, in certain patients neurological symptoms and signs may be the initial, major or only clinical manifestation of the disease. The most common such manifestation is encephalopathy or meningo-encephalopathy,[49,139] but Guillain-Barré syndrome,[60] cranial nerve palsies, isolated tonic-clonic seizures and paraparesis have been described.[139] As specific tests of anti-Epstein-Barr virus antibody have been developed, so it has been realized that Epstein-Barr virus infection is implicated in many acute neurological illnesses in young patients and that in these cases heterophile antibody tests are often negative and there are sometimes no manifestations of classic infectious mononucleosis.[62]

The first patient described here had fever, rash, adenopathy and a positive Paul-Bunnell test, but the dominant feature was his neurological disease. The second patient had minimal systemic features and a negative Paul-Bunnell test but a raised titre of antibodies to the D component of early Epstein-Barr virus antigen, a test considered specific for new or re-activated Epstein-Barr virus infection in the absence of lymphoma, leukaemia, other malignant lesions or cytomegalovirus infection.[66] Ideally IgM antibody to viral capsid antigen should also be measured[66] but this test was not available in Cape Town at the time the patient was admitted. These cases support the assertion of Silverstein et al[139] that Epstein-Barr virus infection should be considered in any young patient with an acute

neurological illness.

The prognosis of neurological complications of Epstein-Barr virus infection is good.[53] If the patient can be supported through the acute illness, excellent recovery is usual. Most series report complete resolution of encephalitis even when decorticate rigidity is present[134] and show a similar outcome for the Guillain-Barré syndrome. In some cases residual weakness remains after acute myelopathy, but this has been mild.[139] The first patient started to recover from almost complete paralysis on the 9th day of his illness and thereafter improved slowly over 9 months to almost full recovery. The second patient showed dramatic improvement after only 2 days and power was normal by 7 days.

7.3. Other infections

Acute myelopathy has also been documented as a rare complication of measles, rubella, mumps,[109] chicken-pox[107] zoster[25] and infection with herpes simplex,[95] cytomegalovirus[90] and echovirus.[88] The pathogenesis of the myelopathies is not established - most are probably para - or post - infectious hypersensitivity reactions, but some may be due to direct viral infection. Herpes simplex[95] and echovirus[88] have been grown from CSF in myelopathies and 1 autopsy study[74] showed viral inclusion particles in spinal cord tissue and grew herpes zoster from the material.

The clinical pictures are non-specific with the CSF usually showing a raised protein concentration and lymphocytic pleocytosis. Occasional cases with low CSF glucose concentration have been reported in cytomegalovirus[90] and herpes simplex[95] infections.

Apart from viruses, acute myelopathy is reported in tetanus,[12] rickettsial infection,[124] schistosomiasis,[20,127] toxocara infection[157] and trichinosis.[124]

8. SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) RELATED MYELOPATHY

8.1. Case reports

Two patients developed myelopathy in association with probable SLE.

Case No.15.

A previously well 26 year old black male developed fever, nausea, vomiting and malaise in December 1983. This was followed by the gradual onset of progressive leg weakness. Two weeks later his power worsened markedly. He developed urinary incontinence and arm weakness and over 5 days became completely quadriplegic. There was no backache.

General examination was normal. Cranial nerves were normal except for mild palatal weakness. There was a complete quadriplegia with general hyperreflexia and a left extensor plantar response. Sesnsation was lost to all modalities below C_4 bilaterally. There was an atonic anal sphincter and urinary catheterisation was required.

Chest X-ray, spinal X-rays and myelogram were normal. CSF on admission (3 days after the start of his more rapid deterioration) showed a protein concentration of 1 g/l, 2 + globulin, 6 neutrophils, 54 lymphocytes mm^{-3} and CSF glucose concentration of 1,6 mmol/l (29% of blood glucose concentration), CSF IgG albumin ratio and the IgG index[129] were normal. All stains and cultures were negative as was syphilitic serology.

Blood haemoglobin concentration and leucocyte count were normal but there was a persistent lymphopaenia ($468 \times 10^9\ \ell^{-1}$ and $920 \times 10^9\ \ell^{-1}$) before corticosteroid therapy. There was no significant proteinuria and renal function was normal. Anti-nuclear antibody titre during the patient's

hospital stay ranged between 20 and 500. Anti-DNA antibody levels were raised between 15 and 27 micrograms DNA bound per ml of serum (normal <10). Rheumatoid factor was negative and serum complement concentration normal.

The patient developed respiratory difficulty necessitating tracheostomy and supportive ventilation. He was commenced on 60 mg Prednisone daily. Six weeks after admission he had regained some power in his arms, bulbar function was normal and ventilation was no longer required. A repeat LP three months after admission was normal. By the time of discharge 7 months later, he had only mild arm weakness but remained with a dense spastic paraplegia with a T_9 sensory level.

Comment

This case illustrates a severe myelopathy in a previously well patient associated with persistent lymphopaenia, raised anti-nuclear factor and raised anti-DNA antibodies. Of note are the sudden worsening after a gradual start, the low CSF glucose concentration and the recovery of arm function.

Case No. 16.

In May 1971 a previously well 51 year old white female developed an illness characterized by fever, polyarthritis and bilateral pleural effusions. LE cells were found on 2 occasions. She was treated successfully with corticosteroids.

She was then well until May 1978 when she noticed a slight weakness of her feet. About 7 weeks later she noticed that her right leg felt hot and numb and became weaker. Five days later she developed a similar sensation and weakness in her left leg.

Abnormal physical findings were limited to the legs. The legs were

asymmetrically weak with grade 3/5 power in the left and 4+/5 power in the right. Both legs were hypertonic and hyperreflexic. The left plantar response was extensor. There was bilateral disturbance in touch, pain and temperature sensation, but more marked on the right. Position sense was lost only in the left foot.

CSF examination showed a protein concentration of 0,1 g/l and no cells. CSF IgG albumin ratio and Lange colloidal gold curve was normal and syphilitic serology was negative. Chest X-ray and spinal X-rays were normal except for mild cervical spondylosis. A myelogram was not performed as the patient recovered. Hb concentration and blood leucocyte count was normal. The rheumatoid factor, antinuclear factor, anti-DNA antibodies and tests for LE cells were all negative.

Prednisone therapy was commenced. Three weeks after admission, power and sensation had markedly improved. By January 1979 only a burning sensation in the right leg remained with no objective physical signs. Telephonic follow-up in October 1984 revealed no further illnesses but a persistent dysaesthesia in the right leg.

Comment

This patient illustrates the development of a partial Brown-Séquard syndrome in a patient who 7 years earlier had a multi-system illness with polyarthritis, pleural effusions and positive LE cells. Of note are the slow onset with worsening after 7 days, a normal CSF, a negative test for auto-immune disease during the myelopathy and excellent recovery.

8.2. Discussion

The reported frequency of clinical neuropsychiatric involvement in SLE varies between 28 and 37%,[11,22,44,] the commonest manifestations being

psychoses and seizures.[44] In one autopsy study, CNS involvement was found pathologically in 75%[89]. Spinal cord diseae, however, is uncommon and accounts for between 1 and 7% of neuropsychiatric manifestations in large series.[22,44,89,135] One smaller study of 13 patients found a 15% frequency of myelopathy.[141]

Approximately 30 cases of SLE related myelopathy have been described. The larger series are those of Penn and Rowan (1968),[121] Fulford et al.(1972)[50] Adrianakos et al.(1975)[9] and Kewalramani et al. (1979)[93] accounting between them for a total of 16 patients. The following summary is based on an analysis of 27 patients in the literature described with adequate clinical details and the 2 patients in the present study.

8.2.1. Clinical aspects

The formal diagnostic criteria for SLE are laid down in the 1982 revised criteria of the American Rheumatism Association.[145] However, these criteria are designed to differentiate SLE from other collagen vascular disorders and thus are not always appropriate for the diagnosis of SLE as a cause of neurological disease. For instance only seizures and psychoses are permitted as neurological criteria for diagnosis and thus the myelopathy itself cannot be counted. Of the 27 patients in the literature, only 14 have the required 4 or more criteria. Both patients in the present series had 3 criteria (lymphopaenia, raised anti-nuclear factor and raised anti-DNA antibodies in case 15 and polyarthritis, pleural effusions and positive LE cells in case No. 16).

Myelopathy may occur as the presenting manifestation of SLE,[50,56,137] or at any stage in the disease. Case No. 15 in the present study illustrates the disease manifesting initially as a myelopathy. This patient

is of special interest because of the rarity of SLE in South African blacks.[148]

The duration of symptoms of myelopathy from onset to maximum varies from 8 hours[93] to years.[50] Seven out of 29 patients (24%) had hyper-acute onsets with progression over less than 12 hours[64,93,121] and 3 others progressed in less than 3 days.[8] At the other end of the spectrum, all 5 of the patients of Fulford et al[50] progressed for longer than 6 months. Of interest is one patient of Hachen and Chantraine[64] who developed a slowly progressive paraparesis over 6 months and then acute paraplegia over 8 hours. In the present series both patients progressed slowly over weeks and then more suddenly over days.

The clinical picture is as variable as the time sequence. It can vary from a complete quadriplegia[94] to a complete paraplegia[46] to a milder spastic paraparesis.[50] In general, the more hyper-acute cases had more extensive signs. Sensation can vary from normal,[50] through dissociated loss[32,89,93] to absence of all modalities.[56] In a few patients cerebral symptoms occurred simultaneously e.g. seizures and loss of consciousness.[64] Of special interest is that 2 of the 29 patients[10,94] developed Devic's syndrome and 1 other patient is alluded to in the literature without description.[44] Case No 15 in the present series developed a complete quadriplegia losing all sensation whereas case No 16 developed a milder paraparesis with a Brown-Séquard pattern.

Only three of the 29 patients made good recoveries (including case No 16 in the present series).[56,137] Twenty did not improve including 6 who died. One patient (case No 14 in the present series) improved partially from a quadriplegia to a paraplegia. The remaining 5 patients (18%) followed a

relapsing course of partial recovery and secondary deterioration,[64,89,121,147] one patient relapsing twice.[121] Two of these patients died. The time between the first and second episodes was 3-10 months in four patients and 5 years in the fifth. In general the prognosis for recovery is poor - the majority of those who improve tend to relapse.

8.2.2. Laboratory findings

Only 1 patient (case No 15 of the present series) out of 24 whose CSF results are quoted, had completely normal CSF. One other patient had an abnormal Lange colloidal gold curve[50] but no other abnormalaities.

In 13 patients both CSF protein concentration and leucocyte count were raised, while in 9 patients protein concentration alone was raised with no pleocytosis. One patient had a pleocytosis with normal CSF protein concentration.[89] Protein concentrations ranged up to 5,85 g/l but the majority were between 0,5 to 2,0 g/l. The CSF's in all but 2 patients[46,64] had fewer than 500 cells $mm.^{-3}$ CSF glucose concentration was low in 9 patients (32%) including case No 15 of the present series. Adrianakos et al.[9] suggests that this may be a fairly specific finding for SLE myelopathy, especially if the LP is performed on the day of onset of the illness. However, as discussed earlier, patients with syphilitic myelopathy may also rarely have low CSF glucose concentrations as may some with infections such as mycoplasma and cytomegalovirus. Five patients[46,50,56] are reported with first zone Lange colloidal gold curves.

Fulford et al.[50] described 5 patients with a more chronic myelopathy as an early or initial manifestation of SLE. As this resembled multiple sclerosis, they suggested the term "lupoid sclerosis" for the group. They

felt that a fairly specific laboratory picture of raised serum IgM concentration, abnormal serum anti-mitochondrial antibody concentration, negative rheumatoid factor and raised CSF protein concentration with a first zone Lange curve existed. This pattern has not been confirmed.

8.2.3. Pathology

The pathology is not uniform. The most common findings are cord necrosis, often haemorrhagic, involving grey and white matter, associated with vasculitis with thrombosis of the small arteries and veins in the affected area.[9,46,123] In this group small vessel vascular occlusion and secondary infarction appears the major pathogenetic mechanism. However, patients have been described with similar cord necrosis and yet normal vasculature.[89,121] One patient had a necrotic myelopathy with normal vessels and associated optic nerve demyelination.[10] These cases are similar to many of the patients with idiopathic necrotic myelopathy with normal vessels. Presumably an auto-immune process against myelin and neural tissue is responsible.

Two cases quoted by Kewalramani et al.[93] had subdural spinal haematomas secondarily compressing the cord, presumably due to haemostatic disorders. Many patients had subclinical intracerebral pathology in addition, usually haemorrhages or small infarcts.[89,123]

Another vasculitic illness that can present with acute myelopathy, often relapsing, is granulomatous angiitis of the nervous system. Diagnosis can be difficult and may require leptomeningeal biopsy.[30,128] Myelopathy has also been reported in mixed connective tissue disease.[158]

8.2.4. Conclusions

1. Myelopathy is an uncommon neurological manifestation of SLE.

2. Certain patients with myelopathy and positive immunological tests for SLE may not have many extra-neurological manifestations especially at initial presentation. Others can develop myelopathy during the course of obvious SLE.

3. Twenty-five percent of patients have hyper-acute onsets of myelopathy, suggesting a vascular pathogenesis. Other patients progress more slowly, some over years.

4. Prognosis is generally poor, with at least half the patients who improve relapsing usually months later. The mortality rate is high (25-30%)

5. CSF is usually abnormal with either a high protein concentration alone or in association with a pleocytosis. CSF glucose concentration is low in at least 1/3 of patients and perhaps more if LP is performed early.

6. The pathology is usually cord necrosis due to endarteritis, but some patients undoubtedly have necrosis and demyelination without vasculitis suggesting an immunological reaction against myelin or neural tissue.

9. ATHEROMATOUS SPINAL CORD INFARCTION

One patient had an obvious ischaemic myelopathy following emergency surgery for a ruptured aortic aneurysm.

9.1. Case report (case no 17)

A 52 year old white male with a background of hypertension and angina underwent emergency abdominal surgery on 15th November 1982. At surgery an aortic/common iliac artery aneurysm was found with posterior rupture. This was resected and the left renal vein divided. His course post-operatively was complicated by persistent hypotension, acute tubular necrosis and a myocardial infarct.

One week after surgery he noticed he could not move his legs. Neurological examination revealed flaccid areflexic legs with grade 1/5 power in the left leg and grade 2/5 on the right. Plantar responses were not elicitable and the lower abdominal reflexes were absent. There was absent pain sensation below L_1 on the right and L_3 on the left. Position sense was absent in at least the left foot.

One week later the signs were unchanged. He died 25 days after surgery in refractory shock. The spinal cord was not examined at autopsy.

Comment

This case represents a lumbo-sacral myelopathy following surgery for a ruptured aortic aneurysm followed by persistent hypotension.

9.2. Discussion

The rarity of atheromatous spinal cord infarcts is underlined by the identification of only 1 patient in this series with a definite vascular aetiology.

The blood supply of the spinal cord has already been discussed in detail (see section 4.3.3.). The following anatomico-pathological classification for spinal cord ischaemia is based on that of El-Toraei and Juler.[41]

1. Aorta

A. Dissecting aneurysms.

Myelopathy is a rare complcation but one well documented. It is due to disruption and thrombosis of the origins of the segmental arteries.[70]

B. Surgery for abdominal aneurysms (see below for further details).

C. Atheromatous occlusion of the origin of segmental arteries (discussed earlier in section 4.3.3.).

2. Segmental arteries (intercostal and lumbar arteries).

These can be disrupted during sympathectomy[78] and other procedures.

3. Radicular arteries.

These can be occluded in the intervertebral foramina by trauma, osteomyelitis, tuberculous vertebral disease and neoplasms.[41]

4. Vertebral artery.

Atheroma and cervical injury including chiropractic manipulation can result in cord ischaemia due to vertebral artery thrombosis.[41]

5. Spinal arteries.

Although an extremely uncommon site of atheroma, the anterior and sometimes posterior spinal arteries can be involved in inflammatory processes as discussed earlier or by emboli. One well-documented case of a cholesterol

embolus to the anterior spinal artery resulting in a cord infarct has been described.[99]

6. Central intraspinal artery and pial arteries.

These can be involved in inflammatory processes as discussed earlier.

Ischaemia from all these mechanisms can be worsened by concomitant hypotension.[45,85]

The clinical pattern of atheromatous cord infarcts has already been discussed (see section 4.3.3.)

Spinal cord ischaemia following abdominal aortic aneurysm surgery is well-documented but rare. Ferguson et al. reviewed 29 cases in the literature.[45] In all cases the upper level of the myelopathy was below T_9 and in most cases it was purely a lumbo-sacral problem. Twelve occurred after elective surgery and 17 followed emergency surgery for a ruptured aneurysm.

Two groups were identified with respect to outcome - in some patients partial or complete recovery occurred suggesting ischaemia as the major mechanism, while in others the deficit was permanent suggesting cord infarction. Probably the pathogenesis is multifactorial with hypotension, resection of a a significant segmental artery and emboli to spinal arteries all being significant. In the patient reported here, prolonged hypotension followed surgery.

10. MISCELLANEOUS CAUSES

As mentioned earlier, acute myelopathy has been associated with drugs and toxins (see section 4.3.3.).[55,124] The Japanese condition of Subacute Myelopathy and Optico-Neuropathy (SMON) is thought to be due to Iodoxyquinoline toxicity.[124]

Acute necrotic myelopathy is one of the rarest of paraneoplastic conditions. Radiation myelopathy and secondary deposits must first be excluded. The condition has been described with carcinoma of the lung, stomach, ovary, thyroid and prostate, as well as in lymphoma (Hodgkin's and non-Hodgkin's types). One patient with non-Hodgkins' lymphoma developed neuromyelitis optica.[67,112]

Sarcoid can be complicated by a chronic myelopathy and extremely rarely by an acute one.[16]

None of these conditions were seen in the present study.

11. CONCLUSION

This study has analysed the spectrum of acute and subacute myelopathy over a 7½ year period as seen in a South African teaching hospital. Some general conclusions are formulated here.

The first aim of the study was to analyse the spectrum of conditions responsible for the syndrome. A specific aetiology was found in 50% of cases. By far the most common was a relationship to infectious disease (45%). Meningo-vascular syphilis comprised half of these cases, while a presumed immune reaction to other systemic infections (PTB, Mycoplasma and Epstein-Barr virus) the remainder. The other 5% comprised vasculitic illnesses (SLE) and atheroma related cord infarction. All these conditions should be looked for in any patient presenting with acute cord disease.

The second aim was to categorise the conditions clinically and to correlate the clinical findings with aetiology. Each aetiological group has been discussed separately but a few aspects are highlighted. In the idiopathic group the presence of partial cord syndromes and the relationship to brainstem disease has been more clearly delineated. The clinical picture of syphilitic myelopathy does not appear to have changed significantly since penicillin therapy became available. The relationship of PTB to Devic's syndrome is of considerable interest and has been discussed fully.

The third aim was to assess the diagnostic criteria for the syndrome. This study has broken away from empirical criteria previously used for the diagnosis of "transverse myelopathy". This approach has revealed the wider spectrum of the condition. In each specific category diagnostic criteria are discussed in more detail. In particular a classification for the laboratory

diagnosis of meningo-vascular syphilis is proposed.

The fourth aim was to correlate previous studies with the present one. Six previous studies of acute myelopathy have been reviewed, but the vast majority of cases discussed in these studies are idiopathic. These studies and others of more specific aetiological groups have been compared with the present one and differences and similarities analysed.

In summary, this study has attempted to present a comprehensive clinical review of an important and little studied group of conditions.

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